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ENVIRONMENTAL HAZARD ASSESSMENT OF ONE AND TWO CARBON FLUOROCARBONS

SYRACUSE UNIVERSITY

PREPARED FOR
ENVIRONMENTAL PROTECTION AGENCY

SEPTEMBER 1974

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ENVIRONMENTAL HAZARD ASSESSMENT
OF
ONE AND TWO CARBON FLUOROCARBONS

SEPTEMBER 1975

FINAL REPORT

OFFICE OF TOXIC SUBSTANCES
U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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This report reviews the potential environmental hazard from the commercial use of large quantities of saturated, one and two carbon fluorocarbon compounds which are used for the most part as aerosol propellants, refrigerants, solvents, foaming agents, and fire extinguishing agents. The following seven compounds were of major interest: trichlorofluoromethane, dichlorodifluoromethane, chlorodifluoromethane, trichlorotrifluoroethane, dichlorotetrafluoroethane, chloropentafluoroethane, and bromotrifluoromethane. Information on physical and chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination as well as information related to health and biological effects are reviewed.

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ENVIRONMENTAL HAZARD ASSESSMENT
OF
ONE AND TWO CARBON FLUOROCARBONS

September 1974
Final Report
Contract No. 68-01-2202
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Project Officer
Farley Fisher

Prepared for
Office of Toxic Substances
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COMMERCIAL FLUOROCARBON AEROSOL PROPELLANTS, SOLVENTS, FIRE EXTINGUISHING AGENTS AND REFRIGERANTS

INTRODUCTION

This report reviews the potential environmental hazard from the commercial use of large quantities of saturated, one and two carbon fluorocarbon compounds which are used for the most part as aerosol propellants, solvents, fire extinguishing agents or refrigerants. The major compounds of interest in this report are listed in Table I. Assessments of environmental hazard for a broader spectrum of fluorocarbons are presented elsewhere (Howard and Durkin, 1973; Lutz et al., 1967).

Table I

Major Commercial Fluorocarbons

Chemical	Formula	Flucrocarbon #
Trichlorofluoromethane	CCl_3F	11
Dichlorodifluoromethane	CCl_2F_2	12
Chlorodifluoromethane	$CHClF_2$	22
Trichlorotrifluoroethane	$CCl_2F\text{-}CClF_2$	113
Dichlorotetrafluoroethane	$CClF_2\text{-}CClF_2$	114
Chloropentafluoroethane	$CClF_2\text{-}CF_3$	115
Bromotrifluoromethane	$CBrF_3$	13B1 (H1301)

Information on physical and chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination as well as information related to health and biological effects are reviewed.

Throughout the report a shorthand numerical system will be used instead of the cumbersome but more precise chemical nomenclature. The most common system used by industry and the system utilized in this report consists of a 4-digit number--for example, fluorocarbon ABCD, where D is the number of fluorine atoms in the molecule, C is 1 plus the number of hydrogen atoms in the molecule, B is equal to the number of carbon atoms minus 1, and A equals the number of double bonds in the molecule. Whenever A or B equal zero, the digits are omitted from the number. This system works well with low molecular weight chlorofluorocarbons which are the major commercial products. When bromine is substituted for chlorine, a B plus the number of bromine atoms follows the number of fluorine atoms (e.g., $CClF_3$ is 13 whereas $CBrF_3$ is 13B1). The appropriate numbers for the seven commercially important fluorocarbons are presented in Table I. With the fire extinguisher agents, such as bromotrifluoromethane, a different numbering system (Halon system) is frequently used which results in the number 1301 rather than 13B1: ABCD signifying the number of carbon, fluorine, chlorine, and bromine atoms, respectively. This numbering system is used in discussing the toxicologic literature on fire extinguishing agents. Such numbers are preceeded by an "H" rather than an "F".

I. Structure and Properties

A. Chemical Structure

The fluorocarbons under review are saturated compounds containing one or two carbon atoms and fluorine. Chlorine, bromine, and hydrogen atoms also may be present. Although some refrigerant, solvent and aerosol propellant formulations are mixtures of fluorocarbons, most of the commercial products consist of a pure compound. The chemical formula and molecular weight of these chemicals and the frequently used azeotropic refrigerant mixtures are listed in Table II.

Table II: Physical Properties of Fluorocarbon Compounds
(DuPont, 1969a; Allied Chemical, no date (a); Union Carbide, 1973-4)

Major Commercial Products

Properties		11	12	22	113	114	115	13B1 (FE-1301)	152a	13	500*	502*	503*	Propellant A**	113-MCB***	113-HEP***	113-EA***	113-T***
Chemical Formula		CCl_3F	CCl_2F_2	$CHClF_2$	$CCl_2F-CClF_2$	$CClF_2-CClF_2$	$CClF_2-CF_3$	$CBrF_3$	CH_3CHF_2	$CClF_3$								
Molecular Weight		137.37	120.92	86.47	187.38	170.93	154.47	148.92	66.1	104.5	99.3	111.63	87.5					
Boiling Point at 1 atm	°C	23.82	-29.79	-40.75	47.57	3.77	-39.1	-57.75	-25.0	-81.4		-45.42						
	°F	74.87	-21.62	-41.36	117.63	38.78	-38.4	-71.95	-13.0	-114.6	-28.3	-49.76	-127.6		115.6	97	112	115-180
Freezing Point	°C	-111	-158	-160	-35	-94	-106	-168	-117	-181								
	°F	-168	-252	-256	-31	-137	-159	-270	-179	-294	-216				<-58.0	<-61.0	-3	-96
Critical Temperature	°C	198.0	112.0	96.0	214.1	145.7	80.0	67.0	113.5	28.9		82.2						
	°F	388.4	233.6	204.8	417.4	294.3	175.9	152.6	236.3	83.9	222	179.9	67					
Critical Pressure	atm	43.5	40.6	49.12	33.7	32.2	30.8	39.1	44.37			40.2						
	lbs/sq in abs	639.5	596.9	721.9	495	473.2	453	575	652		642	591.0	632					
Density, Liquid at 25°C (77°F)	g/cc	1.476	1.311	1.194	1.565	1.456	1.291	1.538	0.902			1.217		1.23				
	lbs/cu ft	92.14	81.84	74.53	97.69	90.91	80.60	96.03	56.21			75.95		79.2				
Density, Sat'd Vapor at Boiling Point	g/l	5.86	6.33	4.72	7.38	7.83	8.37	8.71				6.22						
	lbs/cu ft	0.367	0.395	0.295	0.461	0.489	0.522	0.544				0.388						
Specific Heat, Liquid (Heat Capacity) at 25°C (77°F)	cal/(g)(°C)	0.208	0.232	0.300	0.218	0.243	0.285	0.208				0.293						
Specific Heat, Vapor at Const Pressure (1 atm) at 25°C (77°F)	cal/(g)(°C) Btu/(lb)(°F)	0.142 @ 38°C (100°F)	0.145	0.157	0.161 @ 60°C (140°F)	0.170	0.164	0.112				0.164						
Heat of Vaporization at Boiling Point	cal/g	43.10	39.47	55.81	35.07	32.56	30.11	28.38				41.21						
	Btu/lb	77.58	71.04	100.45	63.12	58.53	54.20	51.08				74.18						
Viscosity at 25°C (77°F) Liquid	centipoise	0.42	0.26	0.23	0.68	0.36	0.18	0.155	0.237			0.18			0.68 (68°F)	0.46 (68°F)	0.8	1.0
Vapor (1 atm)	centipoise	0.0106	0.0125	0.013	0.010 (0.1 atm)	0.0112	0.0127	0.0156				0.013						
Surface Tension at 25°C (77°F) dynes/cm		18	9	8	17.3	12	5	4				6			21.2 (75°F)	21.3 (75°F)	19.2 (75°F)	21.0 (75°F)
Refractive Index of Liquid at 25°C (77°F)		1.374	1.287	1.256	1.354	1.288	1.214	1.238				1.235						
Dielectric Constant Liquid		2.28 @ 29°C	2.13 } @ 29°C	6.11 @ 24°C	2.41 @ 25°C	2.26 @ 25°C												
Vapor (1 atm)		1.0036 @ 24°C	1.0032 }	1.0035 @ 25.4°C		1.0043 @ 26.8°C	1.0035 @ 27.4°C											
Solubility of Compound in Water at 1 atm and 25°C (77°F)	wt %	0.11	0.028	0.30	0.017 (Sat'n Press)	0.013	0.006	0.03										
Solubility of Water in Compound at 25°C (77°F)	wt %	0.011	0.009	0.13	0.011	0.009		0.0095 (70°F)				0.056			0.02 (75°F)	0.08 (75°F)	<1.3 (68°F)	0.7 (68°F)
Vapor Pressure at 25°C (77°F)	psia	15	82	150	5.4	31	130	230		510								

*Azeotrope 500 (73.8% CCl_2F_2, 26.2% CH_3CHF_2 by weight)

502 (48.8% $CHClF_2$, 51.2% $CClF_2-CF_3$ by weight)

503 (40.1% CHF_3, 59.9% $CClF_3$ by weight)

**Propellant A ([illegible] [illegible], [illegible] CCl_2F_2, 1% isobutane)

***113-MCB (Azeotrope, $CCl_2F-CClF_2$, $C_2H_2Cl_2$)

113-HEP (Azeotrope, $CCl_2F-CClF_2$, CH_2Cl_2, Cyclopentane)

113-EA (Azeotrope, $CCl_2F-CClF_2$, 96-98 alcohol)

113-T (Blend, $CCl_2F-CClF_2$, $CH_3CH(OH)CH_3$)

The fluorocarbons may also be formulated with non-fluorocarbons. Table III lists some typical blends of fluorocarbons with non-fluorocarbon chemicals. In addition, stabilizers such as nitromethane are sometimes added to alcohol-based aerosols (0.3% by weight).

Table III: Typical Blends of Fluorocarbons with Non-Fluorocarbons
(Union Carbide, 1973-74, p 28)

Blend	Application
45% F-11, 45% F-12, 10% isobutane	Propellant
Azeotrope: F-113 and Dichloroethane	Solvent
Azeotrope: F-113, CH_2Cl_2, cyclopentane	Solvent
Azeotrope: F-113 and SDA-30 alcohol	Solvent
Blend: F-113 and Isopropanol	Solvent

B. Physical Properties

The fluorocarbons usually are characterized by high vapor pressures (low boiling point), high density, low viscosity, low surface tension, low refractive indices, and low solubility parameters. The common physical properties are tabulated in Table II.

The degree of fluorine substitution greatly affects the physical properties. Generally, as the number of fluorines replacing chlorines increases, the vapor pressure goes up, but the boiling point, the density and the solubility parameter decrease. Bromine atoms have a tendency to increase the density and lower the vapor pressure. The vapor pressure/temperature plots for various fluorocarbons given in Figure 1 illustrate the fluorine substitution effect. For example, in the chlorofluoroethane series, vapor pressures increase with fluorination: 112 < 113 < 114 < 115 < 116.

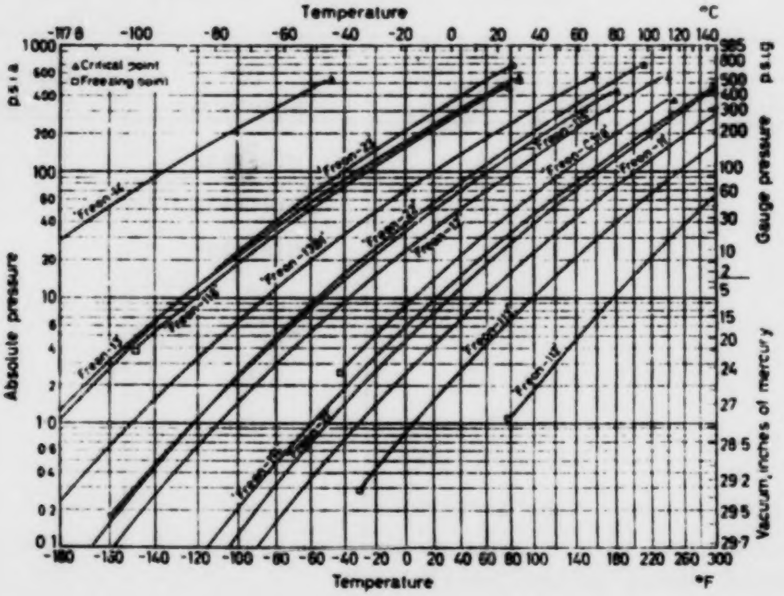

Figure 1

Pressure-Temperature Relationships of Freon Compounds
(DuPont, 1969a)

The solvent power of the fluorocarbons ranges from poor for the highly fluorinated compounds to fairly good for the less fluorinated compounds (DuPont, 1969a). Being typical nonpolar liquids they exhibit low water solubility. The highly fluorinated compounds are generally considered both hydrophobic and oleophobic. Some solubility relationships for fluorocarbons are shown in Table IV. The kauri-butanol test consists of the titration to a cloudy end-point of a kauri-resin dissolved in butanol. The higher the kauri-butanol value, the higher the solvent power.

Table IV: Fluorocarbon Solubility Relationships
(DuPont, 1969a; Union Carbide, 1973-4)

Product	Solubility of Water at 32°F (0°C), % by Wt.	Oil Solutions	Kauri-butanol Number
11	0.0036	Miscible	60
12	0.0026	Miscible	18
21	0.055	Miscible	102
22	0.060	*	25
113	0.0036	Miscible	32
114	0.0026	*	12
502	0.022	*	14 (est.)
113-$C_2H_4Cl_2$	0.02 (75°F)	-	51
113-$CH_2Cl_2C_5H_{10}$	0.02 (75°F)	-	98

*Two Liquid Phases at Low Temperatures.

The low solubility parameter for fluorocarbons allows their use around elastomers without adverse effects of swelling. Comparison of the linear swelling of elastomers with the various fluorocarbons is presented in Table V.

Table V: Swelling of Elastomers by Fluorocarbons and Other Compounds (DuPont, 1969a)

Product	Per Cent Increase in Length at Room Temperature					
	Neoprene GN	Buna N (butadiene/ acrylonitrile)	Buna S (butadiene/ styrene)	Butyl (isoprene/ isobutylene)	Polysulfide Type	Natural Rubber
"Freon" 11	17	6	21	41	2	23
"Freon" 12	0	2	3	6	1	6
"Freon" 13	0	1	1	0	0	1
"Freon" 21	28	48	49	24	28	34
"Freon" 22	2	26	4	1	4	6
"Freon" 113	3	1	9	21	1	17
"Freon" 114	0	0	2	2	0	2
"Freon" 115	0	0	0	0	0.2	0
"Freon" 502	1	7	3	1.6	1.6	4
"Freon" 13B1	2	1	1	2	0	1
"Freon" 114B2	7	7	15	22	1	26
"Freon" C-318	0	0	0	0	0	0
Methyl chloride	22	35	20	16	11	26
Methylene chloride	37	52	26	23	59	34

C. Principal Contaminants in Commercial Products

The commercial fluorocarbons rank among the highest purity organic materials sold in this country (Bower, 1973). The purity of a typical commercial product will commonly exceed 99.9% (Hamilton, 1962). This lack of contaminants is a result of several carefully performed purification steps. In most cases, the starting material and by-products are separated by fractional distillation followed by basic washing and drying over a suitable desiccant. A typical analysis of fluorocarbon-12 is presented in Table VI.

Table VI: Typical Analysis of Fluorocarbon-12 (Bower, 1973)

Fluorocarbon	
12	99.96^{+} vol. %
13	0.010
11	0.002
21	0.003
22	0.017
H_2O	4.5 ppm
Non-volatile	<0.01 vol. %

The predominant isomers of the ethane series (113, 114) are the more symmetrical isomers, e.g. $CCl_2F\text{-}CClF_2$ and $CClF_2\text{-}CClF_2$. Fluorocarbon-113 usually contains no more than a few tenths of one percent of $CCl_3\text{-}CF_3$, while fluorocarbon-114 usually contains no more than 7-10 percent $CCl_2F\text{-}CF_3$ (Hamilton, 1962).

II. PRODUCTION

A. Quantity Produced

The reported total demand for all fluorocarbons in the U.S. in 1973 was 880 x 10^6 lbs. (Chemical Marketing Reporter, 1973), or approximately 0.5% of the total production of synthetic organic chemicals in the U.S. (Drysdale, 1971). The historical trends of production are presented in numerical and graphic form in Table VII and Figure 2, respectively. The world production of fluorocarbons is considered to be approximately twice the U.S. production (McCarthy, 1974).

B. Producers, Major Distributors, and Importers

The major U.S. producers are listed in Table VIII along with the trade names and numbers of their fluorocarbon products and their total plant capacities. Table IX presents a list of foreign manufacturers of fluorocarbons.

In the U.S., the large manufacturers of the basic fluorocarbon compounds distribute the chemicals to large users such as aerosol packaging companies and refrigerator manufacturers. For example, Allied Chemical sells its Genetron refrigerants through wholesalers located around the country (Allied Chemical, no date, a).

C. Production Sites

The product plant locations are listed in Table X and their geographic positions are depicted on the map in Figure 3.

Table VII

Production of Fluorocarbons in the U.S.
(U.S. Tariff Commission, 1961-1971; Stanford Research Institute, 1973)

Compound	Chlorodifluoro-methane		Dichloro-difluoromethane		Trichlorofluoro-methane		Dichlorotetra-fluoroethane		1-chloro-1,1-difluoroethane	
Fluorocarbon #	22		12		11		114		142a	
	(10^9 g)	(10^6 lbs.)	(10^9 g)	(10^6 lbs.)	(10^9 g)	(10^6 lbs.)	(10^9 g)	(10^6 lbs.)	(10^9 g)	(10^6 lbs.)
1961	10.9*	24*	78.5	173	41.3	91	4.1	9		
1962	13.2*	29*	94.3	208	56.7	125	5.0	11		
1963	16.3*	36*	98.4	217	63.5	140	5.4	12		
1964	19.5*	43*	103.4	228	67.1	148	5.9	13		
1965	22.7*	50*	122.9	271	77.1	170	10.0	22		
1966	25.4*	56*	129.7	286	77.1	170	7.7	17*		
1967	26.8*	59*	140.6	310	82.6	182	10.0	22*		
1968	24.9*	55*	147.9	326	92.5	204	7.7	17*		
1969	32.2*	71*	166.9	368	107.9	238				
1970	33.1*	73*	170.1	375	110.7	244				
1971p	36.3*	80*	176.9	390	117.0	258			.091*	0.2*
1972p	36.3*	80*	199.1	439	136.1	300				

*Sales
p - Preliminary

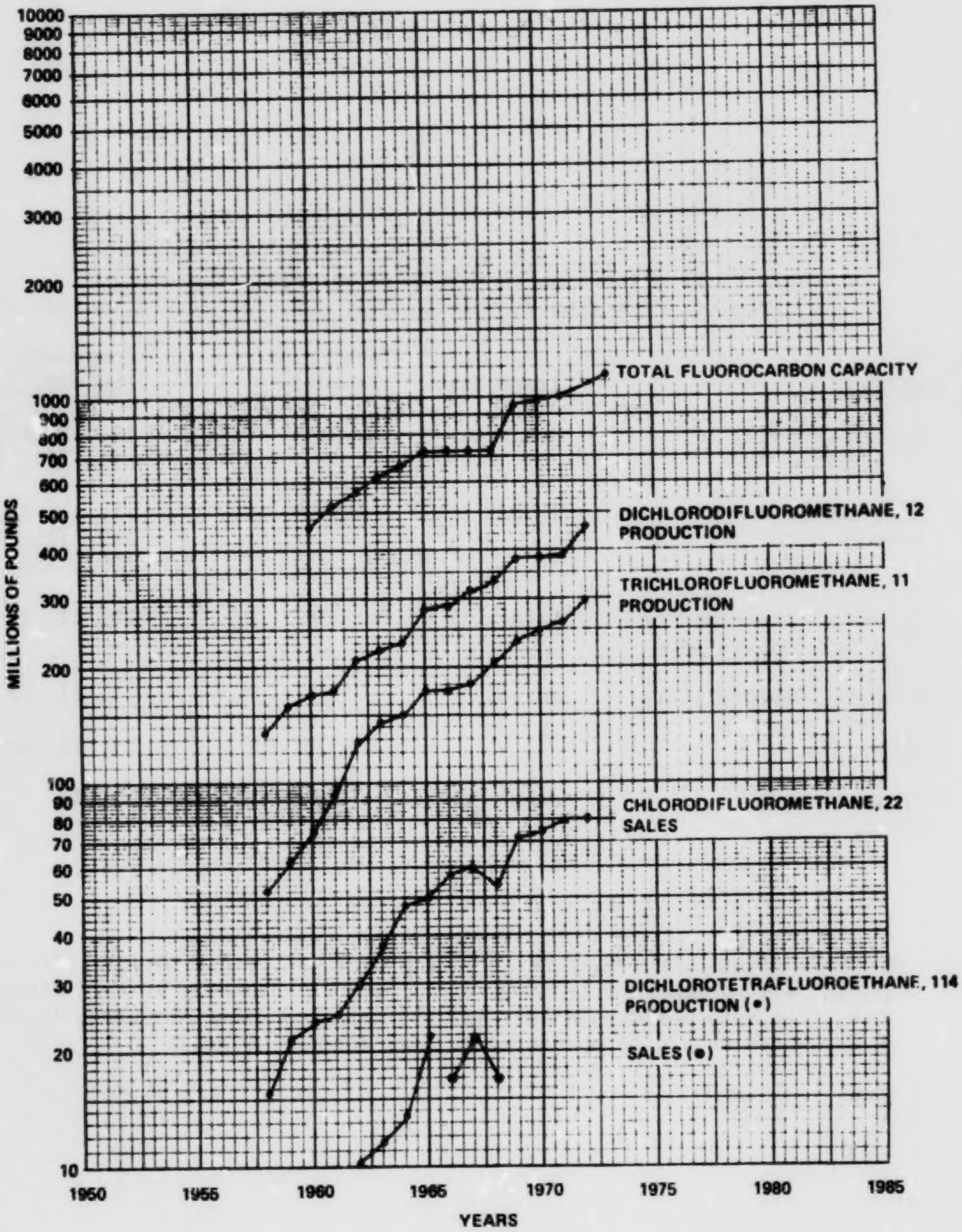

Figure 2

Production and Production Capacity of Fluorocarbons in the U.S. (Stanford Research Institute, 1972; U.S. Tariff Commission, 1961-1972)

Table VIII: Fluorocarbon Producers and Plant Capacities
(Chemical Marketing Reporter, 1973; U.S. Tariff Commission, 1972)

Company	Trade Name	Total Plant Capacity 10^6/yr. in 1973	Compounds Produced
Allied Chemical Corporation	Genetron	310	11, 12, 22, 113, 114, 152a
E.I. duPont de Nemours & Co.	Freon	500*	11, 12, 22, 113, 114, 115, 13B1, 152a
Kaiser Aluminum and Chemical Corporation	Kaiser	50	11, 12, 22
Pennwalt Chemical Corp.	Istron	115	11, 12, 22
Racon, Inc.		20	11, 12, 22
Union Carbide Corporation	UCON	200**	11, 12

*A 500 x 10^6 lbs./yr. facility is being built at Corpus Christi, Texas by DuPont and is expected to be operating at full capacity by 1977 (Anon., 1974b) DuPont is also building a 10 x 10^6 lbs capacity plant for $CBrF_3$ in Deepwater, N.J., which should be operating in 1975 (Anon., 1974c).

**Anon., 1974a.

Table IX: Foreign Fluorocarbon Producers
(Noble, 1972)

Country	Producer
Argentina	Ducilo Siac
Australia	Australian Fluorine Chemicals PTY.
	Pacific Chemicals Industries
Brazil	DuPont Do Brazil
	Fougra
Canada	Allied Chemical of Canada, Ltd.
	DuPont of Canada
England	Imperial Chemical Industries
	Imperial Smelting
France	Ugine Kuhlman
	Perchinery
West Germany	Kali Chemie
	Hoechst
	Von Helyden
	Chemishe Fabrik
	UVB Aleid Fluorowerke
Japan	Daikin
	Mitsui Fluoro
	Asaki Glass
Mexico	Quimobasicos
	Halocarbures
Netherlands	Zinc Organon
	DuPont
	Liquid Nitrogen Processing
	Unichemie
Italy	Montecatini Edison
India	Everst Refrigerant
	Naren Fluorine
South Africa	African Exposives & Chem. Industries
Spain	Kali Chemie
	Electro Quimica de Flix
	Ugine

Table X: Fluorocarbon Production Sites (Chemical Marketing Reporter, 1973)

Company	Location
Allied Chemical Corporation	Baton Rouge, La.
	Danville, Ill.
	Elizabeth, N.J.
	El Segundo, Calif.
E.I. DuPont de Nemours & Co.	Antioch, Calif.
	Carney's Point, N.J.
	Corpus Christi, Texas*
	East Chicago, Ind.
	Louisville, Ky.
	Montague, Mich.
Kaiser Aluminum & Chemical Corp.	Gramercy, La.
Pennwalt Chemical Corp.	Calvert City, Ky.
	Thorofare, N.J.
Racon, Inc.	Wichita, Kan.
Union Carbide Corp.	Institute, W. Va.

*Construction started in the fall of 1973.

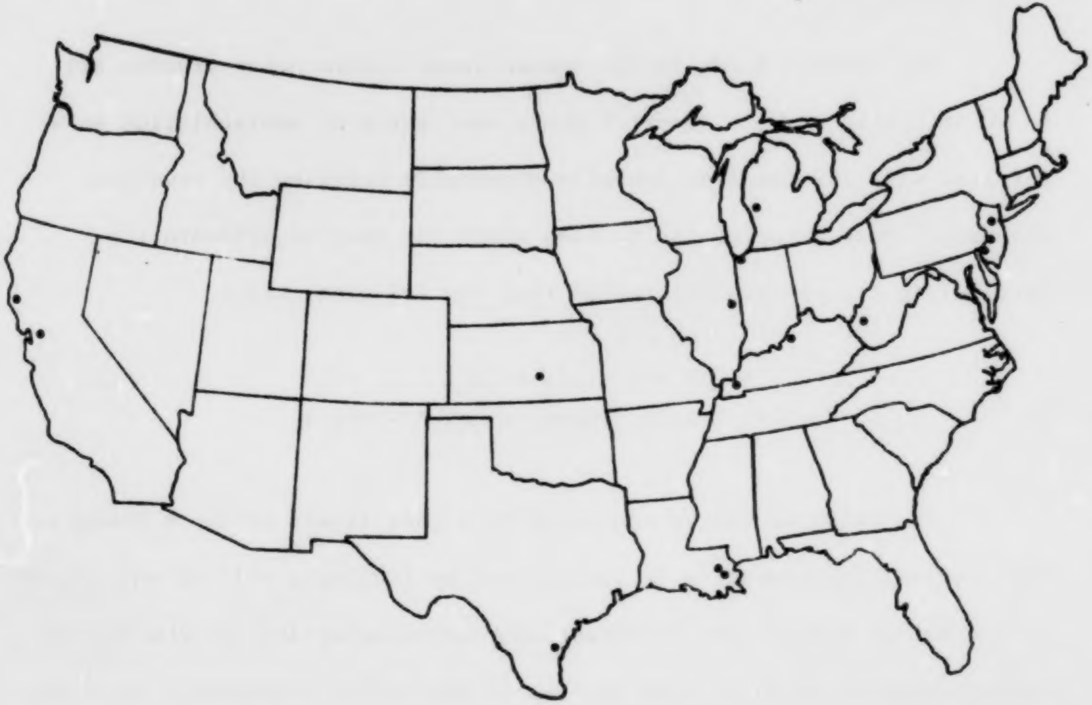

Figure 3

Geographic Locations of Fluorocarbon Production Plants

D. Production Methods and Processes

The most widely used method for commercial synthesis of the major fluorocarbons consists of the catalytic displacement of chlorine from chlorocarbons (commonly CCl_4, $CHCl_3$, and C_2Cl_6 or $C_2Cl_4 + Cl_2$) with fluorine by reaction with anhydrous hydrogen fluoride (Hamilton, 1962). A more recent process developed by DuPont in the U.S. and Montecatini Edison in Italy uses the direct reaction of methane with a mixture of chlorine and hydrogen fluoride. It is reported that this process will be used by DuPont at the plant being constructed in Corpus Christi, Texas (Noble, 1972), but few details are available on the process. However, it has been noted that the process will produce three times the amount of hydrochloric acid which will be converted back to chlorine in a Kel-chlor plant (Noble, 1972).

The several steps in the conventional chlorocarbon process are shown in Figure 4. The reaction phase uses antimony pentachloride as a catalyst with the catalyst actually chemically entering the reaction sequence. Some chlorine gas is also added in order to maintain the catalyst in its pentavalent rather than its trivalent state.

$$SbCl_5 + 3HF \rightarrow SbCl_2F_3 + 3HCl$$
$$SbCl_2F_3 + 2CCl_4 \rightarrow SbCl_5 + CCl_3F + CCl_2F_2$$

The reaction can be conducted in either liquid or vapor phases. The liquid phase operation is carried out by feeding liquid HF and chlorocarbon to the reactor and simultaneously withdrawing HCl and the desired organic product as vapor from the top of the reflux condenser. Reaction conditions can vary from pressures of 0 to 500 psig, temperatures of 45 to 200°C, catalyst concentrations from 10 to 90 wt per cent, and take-off temperatures of -30 to +100°C (Hamilton, 1962). The liquid process is characterized by simple and flexible operation. The quick removal of final product avoids over fluorination.

The vapor phase process consists of a heated tube filled with a granular catalyst. The feed is a vaporized mixture of HF and chlorocarbons. This process is frequently used for the production of the highly fluorinated compounds. In both processes, the proportion of the mixed fluorinated products is determined by the chlorocarbon, and by the temperature, pressure and time considerations.

In all processes by-product hydrogen chloride results. This can be separated either by distillation or scrubbing. The distilled product

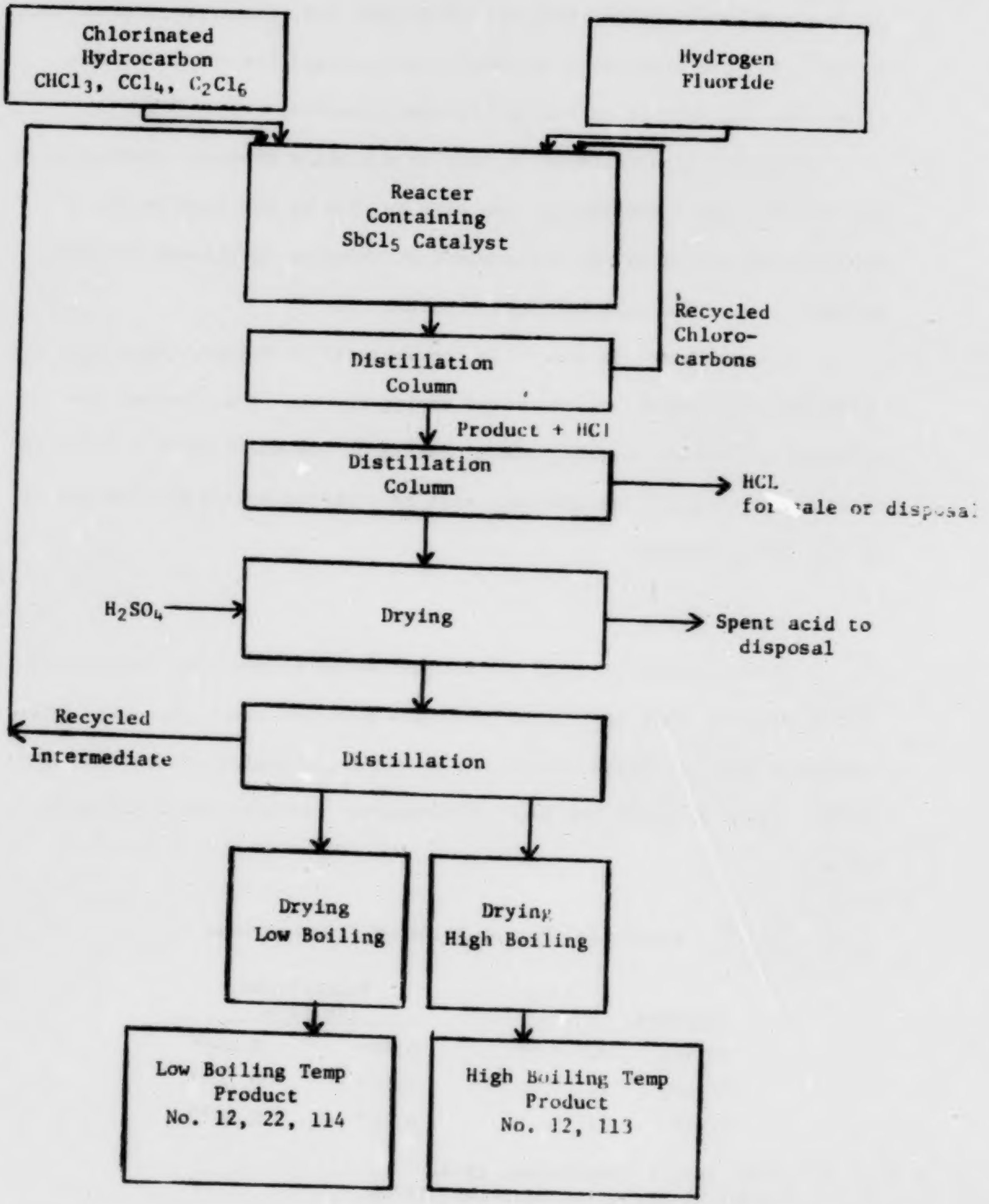
Chlorinated Hydrocarbon $CHCl_3$, CCl_4, C_2Cl_6
Hydrogen Fluoride
Reacter Containing $SbCl_5$ Catalyst
Recycled Chloro-carbons
Distillation Column
Product + HCl
Distillation Column
HCL for sale or disposal
H_2SO_4
Drying
Spent acid to disposal
Recycled Intermediate
Distillation
Drying Low Boiling
Drying High Boiling
Low Boiling Temp Product No. 12, 22, 114
High Boiling Temp Product No. 12, 113

Figure 4

Flow Diagram of Fluorocarbon Manufacture from Chlorohydrocarbons
(Hamilton, 1962; Anon., 1965)

HCl has the advantage of being extremely pure and, therefore, can be used directly in some associated synthesis, or packaged for sale. It also allows the recovery of unreacted hydrogen fluoride.

Bromotrifluoromethane is made by a similar process, starting with the tetrabromide. However, it can also be made by the bromination of trifluoromethane or by the replacement of chlorine in chlorotrifluoromethane by reaction with hydrogen bromide.

The equipment is generally conventional in design, especially the distillation columns, scrubbers and drying towers. The reactors are jacketed or tubular vessels made of carbon or stainless steel. Since the reaction is slightly endothermic, heat is supplied by steam, flue gas or by electrical heaters.

E. Market Price

Fluorocarbon-12, with the largest sales volume, has the current (1973) price in bulk of 29¢/lb. Over the past ten years this has fluctuated between a high of 31¢/lb. and a low of 24¢/lb. (Chemical Marketing Reporter, 1973). Table XI lists the major fluorocarbon products and their market value

Table XI: Market Value of Fluorocarbons

Compound		Value/Pound (dollars)	
$CHClF_2$	22	0.49*	0.48**
CCl_2F_2	12	0.24*	0.34**
CCl_3F	11	0.18*	0.30**

*U.S. Tariff Commission, 1972.
**Chemical Marketing Reporter, 1974b.

III. USES

A. Major Uses

Fluorocarbons are commercially important because of their unique physicochemical properties and relatively low physiological activity. The major applications include uses as aerosol propellants, refrigerants, solvents, blowing agents, fire extinguishing agents, and as intermediates for plastics. Table XII lists the major uses, size of the market, as well as the amount of each fluorocarbon utilized in each application. Plastic intermediates are not included in Table XII since the production figures do not encompass this application. The following paragraphs will briefly discuss the major fluorocarbon applications.

1. Aerosol Propellants

The largest commercial application of fluorocarbons is for propellants in the aerosol* products industry (see Figure 5). The idea of using aerosol propellants dates back to 1863 (Crossland, 1974), but its commercialization did not occur until after World War II. The industry got its start when two USDA researchers found that combining insecticides with liquid refrigerant gases showed an extraordinary increase in insecticide efficiency due to the dispersion as a true aerosol (Hamilton, 1962). During World War II literally millions of the aerosol "bug bombs" were produced.

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*"Self dispensing, pressured, self-propelling products, dispensed by the use of a liquefied, nonliquefied, or noncondensed gas" (Sage, 1963).

Table XII: Uses of Fluorocarbons

Fluorocarbon		Production[d] 1972 (10^6 lbs.)	Aerosol Propellant		Refrigerants		Solvents		Foaming Agent		Fire Extinguishing Agent	
Number	Formula		%[c]	Quantity (10^6 lbs.)	%[c]	Quantity (10^6 lbs.)	%[c]	Quantity (10^6 lbs.)	%[c]	Quantity (10^6 lbs.)	%[c]	Quantity (10^6 lbs.)
11	CCl_3F	300[a]	82	246	3	9			15	45		
12	CCl_2F_2	439[a]	60	264	30	132			10	44		
22	$CHClF_2$	80[a,b]			100	80						
113	$CClF_2CFCl_2$	~50[c]					100	~50				
114	$CClF_2CClF_2$	~20[c]	95	19	5	~1						
115	$CClF_2CF_3$	~10[c]	10	-	90							
13B1	$CBrF_3$				5						95	~4
Total		~900		529		222		50		89		~4
% of Total Production[e]		-		59%		25%		5%		10%		

[a] U.S. Tariff Commission, 1972.

[b] Sales

[c] Estimates based upon discussions with DuPont and Allied Chemical.

[d] The production figures only marginally consider amounts used in the manufacture of fluorocarbon plastics. Fluorocarbon 22, 113, and 114 are used to synthesize the plastics. However, 13 million lbs. of polytetrafluoroethylene was produced in 1972 (U.S. Tariff Commission) from fluorocarbon 22, but that quantity is not reflected in the 80 million lbs. sales figure.

[e] The Chemical Marketing Reporter (1973) reports the following percentage of use: propellants-50%; refrigerants-28%; plastics-10%; solvents-5%; blowing agents, exports, miscellaneous-7% on a 1973 total production of 880 million lbs. The percentages reported in this table are similar in magnitude but quantitatively differ mostly because plastics have not been included.

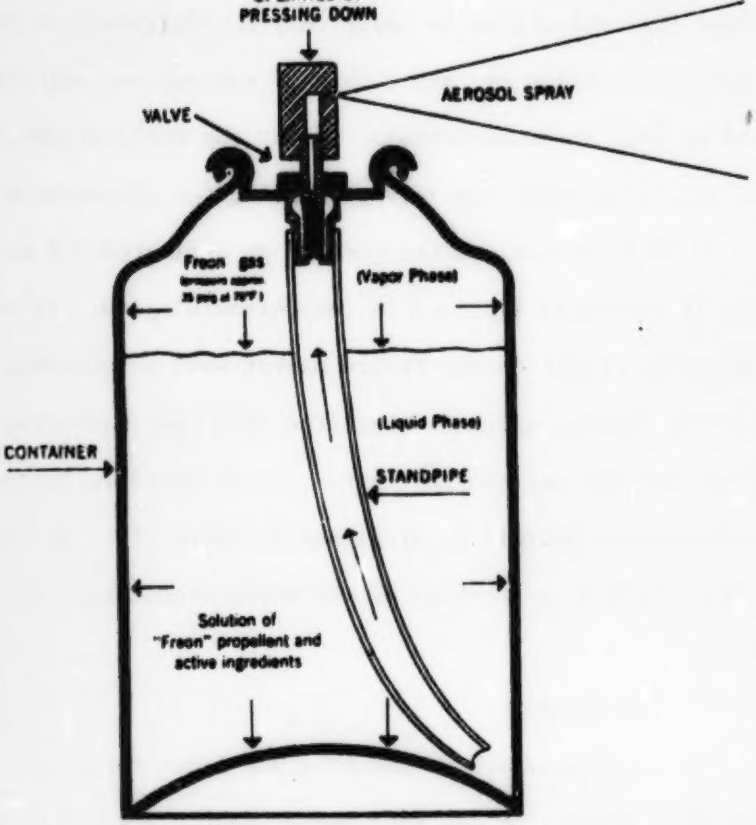

OPERATES BY PRESSING DOWN
AEROSOL SPRAY
VALVE
Freon gas
(Vapor Phase)
(Liquid Phase)
CONTAINER
STANDPIPE
Solution of "Freon" propellent and active ingredients

Figure 5

Cross Section of Typical Aerosol Package
(Sage, 1963)
Permission granted by John Wiley & Sons, Inc.

Civilian commercialization began in the early 1950's after low-pressure valves and nozzles were devised to function below 55 psia and ICC raised its regulations to apply only to containers of 55 psia or more, thus freeing the industry from elaborate control and regulation which are required of high pressure vessels. Today the world production is as much as 6 billion units with the U.S. accounting for approximately 50% of the total. In 1973 the U.S. market grew by an estimated 3.5 to 4% while an increase of 21.4% was reported in the United Kingdom. It is projected that the major growth in the future market will be overseas and a global output of 10 billion units is suggested (Chemical Marketing Reporter, 1974). An aerosol end use pattern in the U.S. is depicted in Table XIII and the global production pattern is displayed in Table XIV. As can be seen from Table XIV, the U.S. percentage of the world production has been steadily decreasing.

2. Refrigerants

The fluorocarbons industry was first founded in the 1930's as a result of a search for new refrigerant gases to replace the highly toxic refrigerant gases being used--e.g., sulfur dioxide and ammonia (Downing, 1966; Crossland, 1973). Their special properties, such as nonflammability, low toxicity, chemical stability, and good thermodynamic properties, made them ideal for use as refrigerants.

This application can be divided into two major categories: (1) refrigeration - localized low temperature cooling; and (2) air-conditioning - cooling of rather large volumes of environmental air. Within each of these

Table XIII: U.S. Aerosol End-Use Pattern
(Chemical Marketing Reporter, 1974)

	1970	1972	1973	1974
Household Products				
Cleaners	155	185	200	210
Laundry Products	200	185	185	190
Room Deodorants	160	180	183	187
Waxes, Polishes	85	100	105	110
Other	30	50	52	53
Total	630	700	725	750
Personal Products				
Colognes & Perfumes	145	135	140	145
Deodorants	480	515	570	595
Hair Care	490	460	460	460
Medicinals	65	65	70	70
Shave Creams	150	165	180	185
Other	50	63	75	80
Total	1,380	1,403	1,495	1,535
All Other				
Automotive	50	80	85	90
Coatings	230	250	255	260
Industrial	90	120	130	145
Insecticides	120	135	140	145
Other	22	35	40	45
Total	512	620	650	685
Grand Total (non-foods)	2,522	2,723	2,870	2,970

Millions of units. Source: Chemical Specialties Manufacturers Association and industry estimates. Food aerosols total in excess of 100 million units annually.

Table XIV: World Aerosol Pattern
(Chemical Marketing Reporter, 1974)

	US, Canada	W. Europe	Others*	World
1974**.	3,185	1,850	765	5,800
1973**.	3,105	1,750	645	5,500
1972.	2,983	1,620	597	5,200
1971.	2,695	1,600	550	4,845
1970.	2,756	1,425	507	4,690
1968.	2,400	1,030	370	3,800

Millions of units. *Includes Australia, Japan, Central and South America and Africa, but excludes USSR and Russian Bloc countries. Source: The Metal Box Company, Risdon Manufacturing Company and Chemical Specialties Manufacturers Association. **Data for 1973-1974 are Chemical Marketing Reporter estimates.

categories, a distinction can be made between prefabricated units, in which the fluorocarbons are charged and sealed at the factory, and large commercial units where the charging is done after the units are in place. In most cases, the distinction corresponds to the size - smaller units being prefabricated while the larger commercial units are filled after placement. The difference between prefabricated and large commercial units is quite important in terms of environmental release because the prefabricated units last an average of ten years, whereas the large commercial units have to be recharged every five years (approximately 80% reclamation of the original refrigerant). Table XV divides the three major refrigerants into the categories mentioned above.

3. Blowing Agents

Blowing agents are used to produce a finished product in a foamed or expanded form. One technique commonly used in the plastics industry consists of dissolving the blowing agent in a plastic and then triggering the gasification by a change in temperature or by a sudden release of a confining pressure (Hamilton, 1962).

Fluorocarbons were first used in the production of polyurethane foams because they impart a significant increase in the thermal insulation properties. They are also used to form open cell foams, in which case the blowing agent is released after its use. Fluorocarbons are divided approximately equally into closed and open cell applications.

Table XV: Use of Fluorocarbon Refrigerants
(Hanavan, 1974)

Fluorocarbon		Quantity Used as	Refrigeration				Air Conditioning			
			Prefabricated		Large Commercial		Prefabricated		Large Commercial	
Formula	Number	Refrigerant (10^6 lbs.)	%	Quantity 10^6 lbs.	%	Quantity 10^6 lbs.	%	Quantity 10^6 lbs.	%	Quantity 10^6 lbs.
CCl_3F	11	9	-	-	72%	6	-	-	28%	3
CCl_2F_2	12	132	45% (automobiles)	59	29%	38	7%	9	19%	25
$CHClF_2$	22	80	57%	46	41%	33	-	-	2%	2
		221		105		77		9		30

% Prefabricated = 52%

% Large Commercial = 48%

4. Solvents

Fluorocarbons find use as a selective solvent for cleaning precision equipment and for extractions of a variety of natural products. With precision equipment, the fluorocarbons, usually 113, provide enough solvent action to remove grease and dirt, but not enough action to swell and damage the plastic and elastomeric components (see Section I). With extraction, the desirable component is separated from the undesirable. A variety of extractions have been reported, including the isolation of edible oils of cotton seed, safflower and soy beans, as well as active ingredients of perfumes, essential oils, spices, coffee and even fish (Hamilton, 1962).

5. Intermediates

Some plastic monomers are made from the basic fluorocarbon compounds. For example, fluorocarbon 22 can be pyrolyzed to form tetrafluoroethylene and hexafluoropropylene. Dechlorination of fluorocarbon 113 yields chlorotrifluoroethylene. The production figures in Table XII do not consider quantities used as feedstocks for fluorocarbon resins. The U.S. Tariff Commission has reported that 13 million lbs. of polytetrafluoroethylene was produced in 1972 (need 15 million lbs. of fluorocarbon 22 assuming 100% efficiency). The Chemical Marketing Reporter (1973) suggests that 10% of 825 million lbs. produced in 1972 are used for plastics. It appears that for 1972 a more plausible figure is 50-100 million lbs. over and above the 900 million lbs. reported in Table XII.

6. Fire Extinguishing Agents

The use of fluorocarbons as fire extinguishing agents is a considerably smaller application than those previously mentioned. The compounds are commonly used in confined areas where it is believed that the chemical acts to extinguish the fire by chain termination of the free radical propagating mechanism of the fire (Hamilton, 1962). An added advantage of these materials is that they present a relatively small threat to life at concentrations and exposure periods necessary to extinguish fires. The fluorocarbon extinguishing agents (collectively referred to as halons) find good application in specialized situations, usually where the value density is high, such as in aircraft, mines, spacecraft, tanks, and computers (Jensen, 1972). The most widely used compound is fluorocarbon 13B1, $CBrF_3$.

B. Minor Uses

Minor applications of the fluorocarbons being reviewed include their use as dielectric fluids, heat-transfer fluids, power fluids, cutting fluids, pressurized leak-testing gases, gases in wind tunnels and bubble chambers, and as a drain opener propellant (DuPont, 1969a; Downing, 1966).

C. Discontinued Uses

The fluorocarbon C318, octafluorocyclobutane, was used as an aerosol propellant with food products. This has largely been replaced by the use of fluorocarbon 115, which has been accepted as a food additive by the U.S. Food and Drug Administration (DuPont, 1969a) [see Section XVI , Current Regulations].

D. Projected or Proposed Uses

There are several applications for the fluorocarbons that could possibly develop into rather large markets for these materials. Both Callighan (1971) and Noble (1972) have noted that the market for the use of fluorocarbons as heat and power transfer fluid has great potential. If the fluorocarbons were adopted for use in the Rankine cycle engine, which uses the same principle as the steam engine, the market would be extremely large, perhaps as large as the total market that now exists (Noble, 1972).

Fluorocarbon-113 is being considered for use in the dry-cleaning solvent market (Noble, 1972; Drysdale, 1971; Lutz et al., 1967). However, it is relatively expensive compared to perchloro- and trichloroethylene and, therefore, the market has not grown appreciably.

Immersion freezing of food with fluorocarbon-12 has also been cited as a potential growth market (Bucholz and Pigott, 1972; Drysdale, 1971; Noble, 1972). Tha boiling point of fluorocarbon-12 (-21.6°F) is ideal for this application.

Another application of possibly large magnitude is contact freezing with brackish water as a desalination process (Stepakoff and Modica, 1973). The hydrolysis rate of the fluorocarbon seems to be the important factor determining whether this application will be commercially significant.

E. Possible Alternatives to Uses

With every commercial chemical, there are two alternatives to its use - (1) substitution with another chemical, or (2) elimination of the use. In order to understand the possibility of either of these two alternatives, one needs to understand what physical and/or chemical properties led to the use of the present compound and what motivated the development of the application. This section will briefly discuss these parameters for the two major applications of fluorocarbons.

1. Refrigerants

The development of the refrigerant industry closely parallels the development of the food preservation and air-cooling industries. Many compounds were evaluated for use as refrigerants but all had serious drawbacks. "Some, like ethylene, were flammable; others, like SO_2, were corrosive and toxic; and still others, like ammonia, combined all three hazards" (Hamilton, 1962). Carbon dioxide was nearly ideal, but necessary high operating pressures made the equipment prohibitively bulky and expensive. In the 1920's a series of fatal accidents traceable to refrigerants led to a development effort to synthesize new chemicals that would overcome the adverse effects described above. Fluorocarbon-12, the first fluorocarbon introduced, was non-flammable and of low toxicity and had a convenient boiling point, -30°C. Thus, the fluorocarbons are used today because they are non-corrosive, non-flammable, have convenient boiling points, and exhibit a low order of toxicity, the last being perhaps the most important. The possibility of these chemicals being replaced by other compounds seems relatively remote.

The possibility of eliminating the need for refrigerants also seems remote. Refrigeration of food is paramount to its preservation both on the way to the consumer and in storage by the consumer. Air conditioning is less a necessity than a convenience, although it was first developed by a physician to cool the rooms of feverish patients. It is a necessity in hospitals and in many industrial operations, such as textiles, paper, photographic film and precision machinery, where climate-controlled air is a requirement. However, air conditioning for residential homes, office buildings, and automobiles is more of a luxury, although some people in tropical and semi-tropical climates would still categorize it as a necessity.

2. Aerosols

The first application of aerosol packaging with insecticides resulted in an increase of efficiency of the active ingredient because it was dispersed as a true aerosol. However, for most products commercially available today, aerosol packaging is not accompanied by an increase in efficiency, and therefore, the packaging is more one of convenience than necessity. Recently, aerosol packaging has come under a great deal of criticism (see Fritsch et al., 1973 and Crossland, 1974).

Fluorocarbons are used as propellants because of their relatively low degree of acute toxicity, non-flammability, inertness toward the active ingredients in aerosol products, and appropriate vapor pressures--i.e., between 15 and 100 psig (Sage, 1963). Table XVI provides a list of possible alternatives to fluorocarbon propellant use. In most cases, the compounds are either flammable or do not have an appropriate vapor pressure.

Other compounds such as methyl chloride, methylene chloride, ethyl chloride, dichloroethylene, and vinyl chloride have been considered as candidate aerosol propellants (Caujolle, 1964), but are considerably more toxic than the commonly used fluorocarbons. In fact, vinyl chloride was shown to cause a rare form of liver cancer and its use in hair sprays and pesticide products has been eliminated (Crossland, 1974). Thus, if one is going to use aerosol packaging, the fluorocarbon compounds seem to be the safest propellant to use. However, exposure to high concentration of fluorocarbons is not recommended (DuPont, 1969b) and the effects of long-term exposure to fluorocarbons have not been completely defined (see Sections XI and XII).

Table XVI: Properties of the Hydrocarbon and Nonliquefied Gas Propellents
(Sage, 1963)

	Propane	Isobutane	η-Butane	Carbon dioxide	Nitrous oxide	Nitrogen	Air
chemical formula	$CH_3CH_2CH_3$	$(CH_3)_2CHCH_3$	$CH_3(CH_2)_2CH_3$	CO_2	N_2O	N_2	$N_2 + O_2$
molecular weight	44.1	58.1	58.1	44.0	44.0	28.0	29
boiling point, °F	-43.9	13.6	30.9	-109[a]	-127	-320	
freezing point, °F	-275	-229	-211				
vapor pressure, psig				837	720	477[b]	
70°F	110	31	16				
130°F	260	96	66				
liquid density at 68°F, g/ml	0.5005	0.5788	0.5571				
heat of vaporization, Btu/lb	183.1	165.6	157.5				
flammable limit, vol. % in air	2.3-7.3	1.8-8.4	1.6-6.5	nonflam	nonflam	nonflam	nonflam
toxicity, UL rating system	5	5	5	5		6	6
solubility in water at 77°F[c]				0.7	0.5	0.014	0.017

[a] Sublimes.

[b] At critical point, -233°F.

[c] Volume of gas at atmospheric pressure soluble in one volume of water.

IV. CURRENT PRACTICES

A. Special Handling in Use

Because the fluorocarbons are commonly used under pressure, the possibility of container explosion always exists. For this reason, containers, especially aerosol containers, should not be exposed to heat. Both injury and death have been reported from exploding aerosol containers that were heated (Fritsch et al., 1973).

Contact with large concentrations of the fluorocarbons should also be avoided. Over 200 deaths from the abusive use of fluorocarbons (getting "high") have been reported (Fritsch et al., 1973). This hazard as well as some other general hazards and some preventive actions are summarized in Table XVII.

Table XVII

Potential Hazards of Fluorocarbons
(DuPont 1969a)

Condition	Potential Hazard	Safeguard
Vapors may decompose in flames or in contact with hot surfaces.	Inhalation of toxic decomposition products.	Good ventilation. Toxic decomposition products serve as warning agents.
Vapors are 4 to 5 times heavier than air. High concentrations may tend to accumulate in low places.	Inhalation of concentrated vapors can be fatal.	Avoid misuse. Forced-air ventilation at the level of vapor concentration. Individual breathing devices with air supply. Lifelines when entering tanks or other confined areas. Do not administer ephinephrine or other similar drugs.
Deliberate inhalation to produce intoxication.	Can be fatal.	
Some fluorocarbon liquids tend to remove natural oils from the skin.	Irritation of dry, sensitive skin.	Gloves and protective clothing.
Lower boiling liquids may be splashed on skin.	Freezing.	Gloves and protective clothing.
Liquids may be splashed into eyes.	Lower boiling liquids may cause freezing. Higher boiling liquids may cause temporary irritation and if other chemicals are dissolved, may cause serious damage.	Wear eye protection. Get medical attention. Flush eyes for several minutes with running water.
Contact with highly reactive metals.	Violent explosion may occur.	Test the proposed system and take appropriate safety precautions.

B. Methods of Transport and Storage

The principal factor required for the transport and storage of the major fluorocarbons is adequate design to meet the elevated pressures. Interstate Commerce Commission Code gives detailed specifications covering the major fluorocarbon chemicals and allowable containers for transport purposes (Du Pont, 1973).

The products are shipped in a wide variety of pressure containers ranging from 5 gallon drums to 20,000 gallon tank cars. The range of sizes and types of containers is as follows:

Nonreturnable steel drums - 5 to 55 gallon
Steel and aluminum cylinders - 1 to 2000 pounds
Tank truck trailers - 2000 to 5000 gallons
Tank cars - 6000 to 20,000 gallons

The containers are fitted with safety valves, rupture discs and fusible plugs according to ICC specifications, as well as requirements for labelling and for leak and pressure testing. The loading or filling limits are also specified for each fluorocarbon in accordance with its physical properties. Procedures for transferring the products between storage and transport facilities are well established by fluorocarbon manufacturers for their own and their customers' operations (Allied Chemical, 1969).

C. Disposal Methods

Disposal of the fluorocarbon products in other than intended purposes (e.g., disposal from propellant use) results principally from the following:

1. Unreclaimed refrigerants in the cooling systems of scrapped prefabricated type refrigeration and air conditioning units. Disposal of these old appliances is usually to scrap yards or waste dumps. With this fate, the refrigerant eventually escapes to the environment by vaporization as a result of corrosion, dismantling or destruction of the units.

2. Products accidentally contaminated in use by customers. When large refrigerator or air conditioner installations are involved, the fluorocarbons are sometimes returned to the fluorocarbon manufacturer for reprocessing, or are purified by the customer by distillation.

Because of the high vapor pressure of all the products at ambient temperature, eventual disposal from the foregoing, as well as from accidental leakage, spillage and from all uses where the compounds are not altered chemically, is to the atmosphere.

D. Accident Procedure

Accidental rupture can be almost completely eliminated by providing appropriate safety valves, rupture discs and fusible plugs. However, when an accident does occur, the following safety precautions should be followed to avoid potential hazards from accidental leakage.

1. Because of their high density, fluorocarbon vapors or gases can accumulate in low confined spaces when accidental releases occur. Provisions for forced ventilation or for use of individual air hoses are required to avoid suffocation or cardiac sensitization in otherwise poorly ventillated areas. Monitoring devices to detect high concentrations should be provided for checking concentrations before entering unventillated areas.

2. To avoid injuries from direct exposure to the chemical escaping from the system, protective clothing, gloves and safety glasses should be used when repairing leaks. The invisible nature of the escaping gas necessitates special precautions.

3. Decomposition of the compounds into toxic chemicals (e.g., phosgene, HCl, HF) can occur if the leaking chemical contacts heated surfaces, sparks or flames, such as occur during welding. Good ventilation and monitoring should be provided if exposure to high temperature is likely. Contact with highly reactive metals should also be avoided as a potentially explosive condition.

V. ENVIRONMENTAL CONTAMINATION

Because of the high volatility and chemical stability of the major fluorocarbons, these chemicals are likely to be released to and persist in the atmospheric environment. Korte and Klein (1971) and Iliff (1972) have briefly discussed the environmental pollution potential from fluorocarbons. This section will (1) estimate the quantities lost from production, transport and storage, use, and disposal; and (2) discuss the general environmental contamination from fluorocarbons and project future contamination levels.

A. Contamination from Production

The production processes described in Section II D give very high yields. Losses are limited to small mechanical leakage, small amounts leaving with byproduct hydrogen chloride, and miscellaneous venting. The total material loss is estimated to be, at the most, 1% (McCarthy, 1973) for the production operations excluding transport and storage. On this basis, the annual losses of fluorocarbon chemicals to the environment from manufacturing operations would be considerably less than 10 million lbs. at current production rates.

B. Contamination from Transport and Storage

The fluorocarbon products are transported in containers having a wide range of capacities (see Section IV B). All containers are designed, tested and labelled according to ICC specifications for pressurized uses. Similarly, storage tanks both at producers' and customers' plants are designed and operated to meet established specifications for the pressure conditions. Procedures for transferring the products between storage and transport facilities are well established (Allied Chemical, 1969).

Loss of product during transport and storage is relatively minor as a consequence of the completely closed system that is used. Losses are further controlled by monitoring discrepancies, if any, between product billings and receipts. In addition, the high cost of the products provides an added incentive to control losses. The total industry-wide loss in transport and storage is judged to be less than 1% of the total quantity of the product handled, or a loss of less than 10 million lbs.

C. Contamination from Use

The major loss of fluorocarbons to the environment is due to their intentional or unintentional release while they are being used. Estimates of loss from the major uses are derived in the following sections.

1. Propellants

The major loss of fluorocarbon products to the atmosphere results from aerosol propellant applications. Essentially, all fluorocarbons consumed by this application enter the atmosphere. It is judged that there is a one-year inventory lag and, therefore, at a growth rate of 6%, the current release is 6% less than production. For 1972 (see Table XII), the loss would be $.94 \times 529 \times 10^6$ lbs. = 496×10^6 lbs.

The predominant method of charging of aerosol containers is a pressure method that is carried out at ambient temperatures. The loss of propellant, which occurs principally while sealing the container, amounts to less than 1% (Harmon, 1974). For 1972, this would amount to a loss of $0.1 \times 529 \times 10^6$ lbs. = 5.29×10^6 lbs., a relatively insignificant amount compared to the loss from the aerosol use.

2. Refrigerants

Loss of fluorocarbons during use as refrigerants may occur in the following ways:

a. charging the refrigerants into the factory sealed prefabricated-type units

b. Loss from abandoned, scrapped, or junked prefabricated-type units

c. Recharging or replacing large commercial and industrial installations with refrigerants.

The loss from (a) is estimated to be about the same order as the mechanical losses at production plants, namely 1%. The demand for prefabricated units is about 52% of the total refrigerant market (see Table XV) and, therefore, the loss from (a) is approximately $.01 \times .52 \times 221 \times 10^6$ lbs. $= 1.15 \times 10^6$ lbs.

Refrigerants in abandoned prefabricated units (b) eventually escape as the parts corrode or are destroyed. The average life for these appliances is at least 10 years, or annually about 10% of the total installed units are scrapped (ASHRAE, 1972a, b, 1973). The total installed units can be calculated by assuming that the total demand is equal to the units lost plus a 6% increase in new units

$$221 \times 10^6 \text{ lbs.} \times 0.52 \text{ (demand)} = 0.06A + .10A \quad (A = \text{total installed units})$$

$$A = \frac{115 \times 10^6 \text{ lbs.}}{.06 + .10} = 720 \times 10^6 \text{ lbs.}$$

Therefore, the amount lost from (b) is 720×10^6 lbs. $\times .10 = 72 \times 10^6$ lbs.

The loss from (c) is judged to be annually about 4% of the total installed units, based on the assumption that the units will be recharged every 5 years and that 80% of the original refrigerant will be recovered. Assuming 48% of the total refrigerant market consists of the large commercial units and using similar reasoning to that described above, the total installed large commercial units can be calculated.

$$221 \times 10^6 \text{ lbs.} \times 0.48 \text{ (demand)} = 0.06A + .04A \quad (A = \text{total installed units})$$

$$A = \frac{106 \times 10^6 \text{ lbs.}}{.06 + .04} = 1060 \times 10^6 \text{ lbs.}$$

Therefore, the loss from (c) is $.04 \times 1060 \times 10^6$ lbs. = 42.4×10^6 lbs.

3. Solvents

It is estimated that the industry-wide efficiency of the recovery systems used with fluorocarbon solvents is approximately 80%. Using an annual growth rate of 6% and a 1972 solvent use quantity of 50×10^6 lbs., the following loss calculation is possible.

$$\text{Loss} = .20 \left(\frac{50 \times 10^6 \text{ lbs.}}{.06 + .20}\right) = 38.5 \times 10^6 \text{ lbs.}$$

4. Blowing Agents

As explained in Section III A, the fluorocarbons used as blowing agents are approximately equally divided between open cell and closed cell applications. Loss from the closed cell foams should be negligible while 100% of the fluorocarbons used for open cell foams should be immediately lost. Therefore, the loss for 1972 should be $.50 \times 89 \times 10^6$ lbs. = 44.5×10^6 lbs.

5. Plastics

Fluorocarbons used as intermediates for plastic monomers probably experience some loss during transport and storage and in the synthesis process. Losses from transport and storage have been considered previously. The loss during synthesis is considered to be negligible.

D. Contamination from Disposal

The release of fluorocarbons to the environment from disposal is principally caused by scrapping prefabricated refrigeration and air conditioning equipment. This has been covered in the section on losses from use.

E. Fluorocarbon Contamination Levels in the Atmosphere

Table XVIII summarizes the fluorocarbon losses for 1972 described in the previous sections. It appears that a substantial amount of fluorocarbons are being released to the environment from use in the U.S. World losses could quite easily double the quantity released.

The high vapor pressure of the major fluorocarbon compounds at ambient temperatures (Section I), the high chemical stability and inertness of the compounds (Section VIII), and the low solubility in aqueous media suggest that a high fraction of the fluorocarbons that are released will accumulate and persist in the atmosphere. This suggestion combined with the fact that sizable quantities of fluorocarbons are being released has prompted a number of monitoring studies, the results of which have been reviewed in Section VII B and are summarized in Table XXI of that section.

Table XVIII: Fluorocarbons Released to the Environment in 1972 from U.S. Applications

Losses From (10^6 lbs.)

Fluorocarbon	Production	Transport & Storage	Uses				Total
			Propellants	Refrigerants	Solvents	Foaming Agents	
11 CCl_3F	3	3	231	~4		22.5	263.5
12 CCl_2F_2	4	4	247	~67		22	344.0
22 $CHClF_2$	.8	.8		~41			42
113 $CClF_2CFCl_2$	~.5	~.5			38.5		40
114 $CClF_2CClF_2$	~.2	~.2	18	~3			22
Total	9	9	496	115	38.5	44.5	711

In this section the extent that the concentrations of fluorocarbon chemicals may increase in the atmosphere during the next 50 years has been projected. In doing this, information on production and use (sections II and III), monitoring data (Section III B), and information on the atmospheric stability of the fluorocarbons (Section X) has been utilized. The projections are based upon the following assumptions:

1. The 1972 annual U.S. production for the several commercial fluorocarbons is approximately as follows: (see Table XII)

	10^6 lbs.
Fluorocarbon 11	300
12	440
22	80
113	50
114	20
115 & 13B1	10
Total	900

2. Distribution by uses are approximately as follows (Table XII combined with Table XV):

Percentage

Fluorocarbon	Aerosol	Refrigeration		Foaming Agent	Solvent	Fire Extinguishing Agent
		Prefab. Units	Large Commercial Units			
11	82		3	15		
12	60	15.5	14.5	10		
22		57	43			
113					100	
114	95		5			
115	10		90			
13B1			5			95

3. Annual growth of each compound has been taken uniformly at 6%. Although the past growth rate has been about 8-10% (8.5% per year for 1962-1972, Chemical Marketing Reporter, 1973), there are indications that the rate is slowing in the U.S.

4. The world consumption has been projected at double the U.S. production. Although the ratio has been less up to the present, it increased from 1.58 in 1968 to 1.75 in 1972 for aerosol use (see Table XIV).

5. Because of the uncertain data on the persistence or residence time of each of the compounds (see Section X), the projections have been estimated only for an infinite residence time in order to give an upper limit value for the concentration.

6. The rate of release of each compound depends upon the use as developed in the preceding sections. These release factors are summarized as follows:

Propellants = immediate except for approximately one year lag due to inventory.

Refrigerants = total loss after 10 years for prefabricated units; for large commercial units the loss is $\frac{42}{106}$ = 40% of the total production used in that application (see Section V, C, 2 annual loss calculation for 1972).

Foaming Agents = 50% is lost immediately (open cell foams); 50% is never lost (closed cell foams).

Solvents = $\frac{38.5}{50}$ or 77% of the new production is lost immediately (see Section V, C, 2 for the annual loss calculation for 1972).

For example, if the total production of fluorocarbon 12 was 100×10^6 lbs., the amount lost immediately would be:

$$100 \times 10^6 \text{ lbs.} \times [\underset{\substack{\uparrow\\ \text{amount}\\ \text{used}\\ \text{for}\\ \text{aerosols}}}{0.60} + \underset{\substack{\uparrow\\ \text{half of}\\ \text{amount}\\ \text{used for}\\ \text{foams}}}{\frac{0.10}{2}} + \underset{\substack{\uparrow\\ \text{amount}\\ \text{used for}\\ \text{large}\\ \text{commercial}\\ \text{refrigeration}}}{(0.145)}\ \underset{\substack{\uparrow\\ \text{amount}\\ \text{lost}\\ \text{from}\\ \text{large}\\ \text{commercial}\\ \text{refrigeration}}}{(0.40)}] = 100 \times 10^6 \text{ lbs.} \times 0.708$$

and ten years later

$$100 \times 10^6 \text{ lbs.} \times .155$$

would be lost from prefabricated refrigeration units (see Table XIX for the calculation of fluorocarbon 12).

7. The volume of the global troposphere is assumed to be 1.8×10^{20} ft.^{3} (5.09×10^{24} ml), based on an average altitude of the troposphere of 30,000 to 35,000 feet, or near the lower limit of the reported range of 25,000-60,000 feet (Van Nostrand's Scientific Encyclopedia). The surface area of the planet was taken as 200×10^6 square miles. The selected height of the troposphere was used in order that the projected results will tend to be conservatively high. The concentration is calculated on a volume/volume basis at standard temperature and pressure.

For the U.S. concentration, the global volume is divided by 4:

$$\text{Concentration in U.S. } CCl_2F_2 = \text{lbs. released} \times \frac{\frac{453.6 \text{ gms}}{1 \text{ lb.}} \times \frac{1 \text{ mole}}{121 \text{ gm}} \times \frac{22{,}400 \text{ ml}}{1 \text{ mole}}}{\frac{5.09 \times 10^{24} \text{ ml}}{4}} =$$

$$\text{lbs. released} \times 6.61 \times 10^{-20}$$

For the global concentration the quantity released is doubled and the total global volume is used.

Table XIX presents the calculations and projected concentrations for fluorocarbon-12. The results of calculations for fluorocarbons 11, 12 and 22, the major commercial products, are depicted in Figure 6. It is felt that these projections are reasonable since the calculated values correspond well with available monitoring data. For example, the calculated average global concentration for CCl_3F is 66 ppt. Lovelock _et_ _al_. (1973) has reported an average concentration of 48 ppt over the Atlantic Ocean. Much higher values were observed (60-80 ppt) in the Northern Hemisphere. The concentration of 97 ppt reported by Su and Goldberg (1973) for CCl_3F in an air sample taken from a desert corresponds well with the calculated U.S. background level of 133 ppt. The slightly higher calculated value may be attributed to the deliberate choice of factors (e.g., atmospheric volume, infinite stability) to project the upper limits of concentration. However, the calculated values do conflict with the CCl_2F_2 concentration of 700 ppt measured by Su and Goldberg (1973) in the desert 100 km northeast of San Diego. We find it hard to believe that the 700 ppt concentration is a background level, especially when this is the average concentration for CCl_2F_2 observed by Hester _et_ _al_.(1973) in the Los Angeles basin and our upper limit calculated value is 133 ppt for the U.S.

Su and Goldberg (1973) have suggested that a longer residence time can explain the higher levels of fluorocarbon 12 than fluorocarbon 11. We have calculated some concentrations using residence times of 10 years for CCl_2F_2(Lovelock et al., 1973) and 30 years for CCl_3F (Su and Goldberg, 1973). These residence times have almost no effect on 1972 concentrations although they have some effect on future projections and, therefore, they do not explain the discrepancy.

Table XIX: Estimation of Average Concentrations of Fluorocarbon 12 in the Atmosphere

Year	Annual Production Rate in U.S. 10^6 lbs.	Total Consumed During 5-year Period 10^6 lbs.	Total Consumed to Date in U.S. 10^6 lbs.	Accumulated Quantity Released to Atmosphere in U.S. (10^6 lbs.)			Concentration in Parts Per Trillion (10^{-12}) by volume	
				Immediate 0.708 x ②	After 10 years .155 x ② 10 years before	Total in Atmosphere no degradation	U.S. Atmosphere	Global Atmosphere
	①	②	③	④	⑤	⑥	⑦	⑧
1952	50	200	200	142	-	142	9	5
		300		212	-			
1957	100		500	354	-	354	23	12
		750		531				
1962	208		1,250	885	31	916	61	30
		1,200		850	46			
1967	310		2,450	1,735	77	1,812	120	60
		1,750		1,240	116			
1972	439		4,200	2,975	193	3,168	209	104
		2,480		1,755	186			
1977	590		6,680	4,730	379	5,109	337	168
		3,320		2,350	271			
1982	790		10,000	7,080	650	7,730	511	254
		4,450		3,150	384			
1987	1055		14,450	10,230	1,034	11,264	745	371
		5,950		4,212	515			
1992	1400		20,400	14,442	1,549	15,991	1057	526
		7,900		5,593	690			
1997	1890		28,300	20,035	2,239	22,274	1472	733
		10,700		7,575	922			
2002	2580		39,000	27,610	3,161	30,771	2034	1012
		14,300		10,124	1,224			
2007	3400		53,300	37,734	4,385	42,119	2784	1385
		19,200		13,594	1,658			
2012	4550		72,500	51,328	6,043	57,371	3792	1887
		25,500		18,054	2,216			
2017	6100		98,000	69,382	8,259	77,641	5132	2554
		34,000		24,072	2,976			
2022	8200		132,000	93,454	11,235	104,689	6920	3444

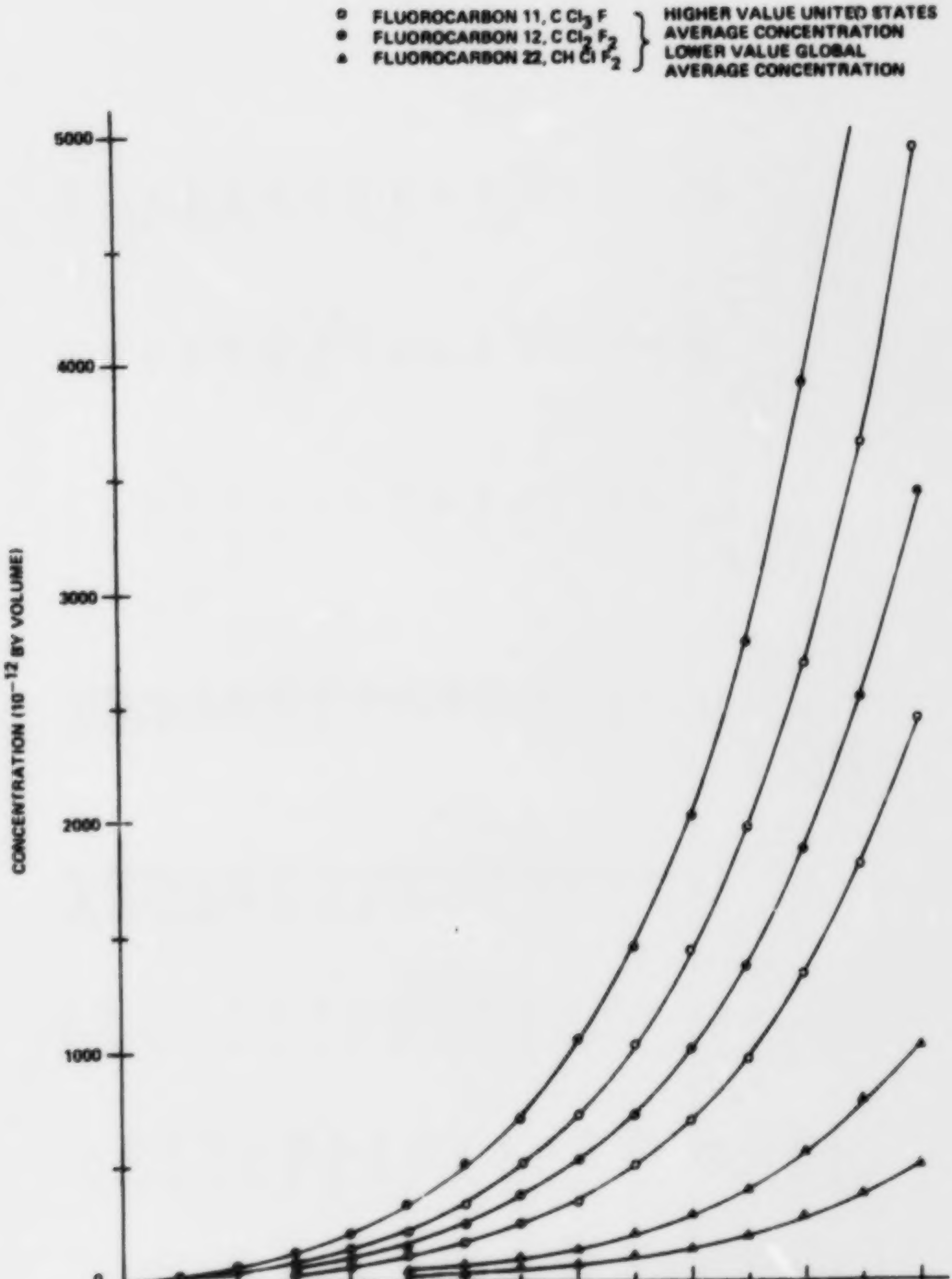


Figure 6 Projections of Average Global and U.S. Atmosphere Concentration of Fluorocarbons 11, 12, and 22

The calculated values are only averages and, therefore, regional fluctuations can be expected. By comparing the variations in 1972-3 monitoring data, it is expected that highly populated centers may have average concentrations 10-15 times the global concentrations (e.g., CCl_3F - global 48 ppt - highest average value measured 650 ppt, Hester *et al.*, 1973). In addition, for short periods of time, concentrations several thousand times the background levels may be observed. Thus, in the year 2000, the average concentration in urban areas of fluorocarbon 11 would be approximately 10 ppb with high fluctuations to possibly 10 ppm.

VI. CONTROL TECHNOLOGY

A. Currently Used

Control technology associated with production, storage, and transport takes the form of preventive maintenance and monitoring for leaks. The industry applies these controls for its own economic benefit. By controlling temperature and pressure a minimum of loss is possible. The monitoring devices can vary from the simplest and oldest technique of using a soap solution to a more sophisticated approach using flame ionization or electron capture techniques.

Loss from use is the major source of fluorocarbon contamination. The major loss is from aerosol propellants and, by its very nature, recovery is impossible. When large quantities of fluorocarbons are used in one place such as in large commercial refrigeration applications or solvent uses, considerable amounts of the materials are recovered by condensation and redistillation. For example, cooling coilings were used to recover solvent loss from a degreasing plant (Greve, 1971). Efficiencies of recovery are kept as high as possible because of the high price of the materials involved.

B. Under Development

No new control technology is under development.

VII. MONITORING AND ANALYSIS

A. Analytical Methods and Sensitivity

Development of analytical techniques for determining fluorocarbons in trace amounts was first undertaken in order to allow the use of fluorocarbons as a tracer of atmospheric dispersion. Schultz (1957) found that dichlorodifluoromethane was a promising tracer chemical. He used a modified ionization-type leak detector which was sensitive to a concentration of approximately 1 ppm; however he was plagued by non-reproducibility (Collins *et al.*, 1965).

Marcali and Linch (1966) reported a colorimetric method for perfluoroisobutylene and hexafluoropropene in air samples capable of detecting these compounds at 0.1 ppm and 0.02 ppm, respectively. The method is based on a chemical reaction between the fluorocarbon and pyridine and piperidine in methanol (collection solvent) due to the unsaturated system ($X-C=CF_2$, X = halogen) and, therefore, is only good for unsaturated fluorocarbons.

McFee and Bechtold (1971) studied a combined pyrolyzer-microcoulomb detector system as a continuous monitoring system. The limits of detection for trichlorotrifluoroethane and tetrachlorodifluoroethane were 0.3 ppm and 0.9 ppm, respectively. The authors suggested that this instrument would be useful for testing air cleaning systems and for measuring toxicants with low threshold limit values.

Shargel and Koss (1972) used a gas chromatographic method with electron-capture detection for determining chlorofluorocarbons in dog blood. The method used a hexane extraction and the lower limits of quantification were 3.3, 10, 40, and 80 μg/l of blood for trichlorofluoromethane, dichlorodifluoromethane, trichlorotrifluoroethane, and dichlorotetrafluoroethane, respectively.

Collins and Utley (1972) studied the possible use of mass spectrometry for detection and identification of organic pollutants in the atmosphere. They used a silicone rubber membrane direct inlet system (similar to GC-MS interfaces) which allowed 1000 fold increases in minor components of air. With this system, they could detect trichlorotrifluoroethane at 0.1 ppm.

Two techniques have been used to detect fluorocarbons in air at ppb to ppt (10^{-9} - 10^{-12}) concentration ranges; (1) direct analysis of air-fluorocarbon mixtures with gas chromatography with an electron-capture detector (GC-EC), and (2) sampling tube concentration with gas chromatography and flame ionization detection (GC-FI). Collins et al. (1965) used the GC-EC technique to study the use of sulphur hexafluoride and dichlorodifluoromethane as gas air tracers. They found the sensitivity for dichlorodifluoromethane to be only in the 50 to 100 ppb range. Saltzman et al. (1966) used a similar GC-EC system with bromotrifluoromethane and octafluorocyclobutane. A sensitivity of about 0.3 ppb was achieved without concentrating the sample.

Gelbicova-Ruzickova et al. (1972) developed a method for determining minute quantities of halothane (2-chloro-2-bromo-1,1,1-trifluoroethane) in the air of operating theaters. They used a porous polymer packing (Porapak P and Q) in a sampling tube to preconcentrate the sample. Detection was carried out with a flame ionization detector (GC-FI). Concentrations down to 10 ppb could be determined. These authors referenced a report that noted a low stability of the electron capture detector if the electrodes are contaminated by large amounts of water vapor and oxygen. However, Lovelock and coworkers (Lovelock, 1971, 1972; Lovelock et al., 1973), Su and Goldberg (1973), and Hester et al. (1973) have found gas chromatography with an electron capture detector to be quite satisfactory for determining trichlorofluoromethane and dichlorodifluoromethane at approximately 5-10 ppt and 100 ppt by volume, respectively (Hester et al., 1973). Lovelock used experimental conditions where the ionization in the detector is complete, making the system coulometric (Lovelock et al., 1971). Lovelock (1971) notes that other fluorocarbons such as difluorodichloromethane and perfluorocyclobutane were not detected at the low background levels because of their low sensitivity in the electron-capture detector. However, higher concentrations of fluorocarbon 12 have been monitored by Su and Goldberg (1973) and Hester et al.(1973).

Clemons and Altshuller (1966) reviewed the electron-capture detector sensitivity of a number of halogenated substances. Table XX lists those results for fluorocarbon compounds and compares them to flame-ionization detection. The figures show that for many compounds (ones with less than 2 chlorines) flame-ionization detection is just as sensitive as electron-capture. However, because the electron-capture detector is specific for halogenated substances, it is often used even when the flame-ionization detector would be more sensitive.

B. Current Monitoring

The sizable quantities of fluorocarbons being released to the environment have prompted a number of ambient air monitoring studies. The first reported monitoring data was a study by Lovelock (1971) that compared the concentration of CCl_3F to the turbidity in southwest Ireland. When the

TABLE XX

Electron-Capture Detector Response to Various Fluorinated Compounds
(Clemons and Altshuller, 1966)

Compound	Fluorocarbon #	Response (sq.in. ppm)	Response Flame-ionization (sq.in. ppm) (all compounds)
SF_6		580	0.1-1.0
$CFCl_3$	11	370	
$(CF_3)_2C=CF_2$	1218	90	
$ClF_2C-CFCl_2$	113	50	
$\underline{CF_2CF_2CF_2CF_2}$	C318	30-40	
CF_3Br	13B1	12-40	
CF_2Cl_2	12	9	
ClF_2CCF_2Cl	114	2	
$CF_2=CCl_2$	1112	0.2	
$CHFCl_2$	21	5×10^{-2}	
CF_3CF_2Cl	115	5×10^{-2}	
$CF_2=CFCl$	1113	3×10^{-2}	
CF_3Cl	13	1×10^{-3}	
CHF_2Cl	22	3×10^{-3}	
CF_4	14	3×10^{-4}	

wind was blowing from the west (Atlantic Ocean) both the CCl_3F concentration (10 ppb by volume) and the turbidity were less than when the wind came from the European continent (CCl_3F concentration 190 ppb). Lovelock (1972) reported similar, but more detailed results of monitoring data in Ireland. When the wind was blowing from the west the average concentration was about 50 ppt; when from the east, 100 ppt. In 1973, Lovelock and coworkers (1973) monitored CCl_3F above the Atlantic Ocean in both the Northern and Southern Hemisphere. A global mean concentration of 48 ppt was reported, with a high in the Northern Hemisphere of 78 ppt and a low in the Southern Hemisphere of 38 ppt. Concentrations in the sea water ranged from 20-70 ppt.

Su and Goldberg (1973) monitored ambient levels of both CCl_3F and CCl_2F_2. In La Jolla and San Diego, California, they found averages of 370 ± 560 ppt and 290 ± 249 ppt for CCl_3F and averages of 5800 ± 4600 ppt and 3200 ± 1400 ppt for CCl_2F_2, respectively. In a desert 100 km north-east of San Diego, they reported 97 ppt and 700 ppt for CCl_3F and CCl_2F_2, respectively.

Hester et al. (1973) monitored CCl_3F and CCl_2F_2 in ambient air samples and in air samples from homes in the greater Los Angeles basin. In ambient air samples the average readings were 560 ppt for CCl_3F and 700 ppt for CCl_2F_2, but the concentrations varied by more than a factor of ten. For each sample, the ratio of CCl_3F/CCl_2F_2 was compared. If the changes in concentration were due only to dilution, the ratio should be fairly constant. However, the ratios varied as much as the concentrations. The average ratio of CCl_2F_2/CCl_3F (1.29) corresponded to a weight ratio of 1.1 gram CCl_2F_2 to 1 gram of CCl_3F. The effects of altitude clearly showed that the fluorocarbons were trapped by an inversion layer (above inversion $CCl_3F \sim 80$ ppt; $CCl_2F_2 = <100$ ppt) as were the visable pollutants. Concentrations of fluorocarbons near a cosmetic plant were only 3-4 fold over typical ambient levels suggesting that the loss suffered in filling aerosol cans is small. Monitoring near a polyurethane plant showed similar low results suggesting small losses from closed-cell foaming operations. The levels of both fluorocarbons 11 and 12 in homes, are, on the average higher than the typical ambient air samples. In some cases, the concentrations were several thousand times higher (CCl_3F range 220-1200 ppt; CCl_2F_2 range 300-510,000 ppt).

Simmonds et al. (1974) also monitored CCl_3F in the Los Angeles basin. They reported an average level of 650 ppt and a lower concentration of 110 ppt when the wind was blowing in from the Pacific. The highest concentration for CCl_3F was observed at 8 a.m., which the authors suggest is due to the early morning use of aerosol propellants. In a few measurements of CCl_2F_2 the authors found similar variations in concentration with time, again suggestive of aerosol dispensers as the source (many aerosols used a propellant mixture of 50:50 CCl_3F/CCl_2F_2). Above an inversion, the authors found a concentration of 260 ppt.

The above monitoring data is summarized in Table XXI.

Table XXI. Fluorocarbon Concentrations in the Atmosphere (ppt, 10^{-12}, by volume)

Reference	Above the Ocean	Above Land Wind from Ocean	Above Land Rural	Above Land Urban	Above Land Desert	In Homes	Above an Inversion
Lovelock, 1971 (CCl_3F)		10	190				
Lovelock, 1972 (CCl_3F)		50	100				
Lovelock *et al.* 1973 (CCl_3F)	48 (aver) 78 high 38 low						
Su & Goldberg, 1973 (CCl_3F)				aver. 370 ± 560 aver. 290 ± 240	97		
(CCl_2F_2)				Aver. 5800 ± 4600 Aver. 3200 ± 1400	700		
Hester *et al.* 1973 (CCl_3F)				Aver. 560		220-12,000	$\sim$80
(CCl_2F_2)				Aver. 700		300 - 510,000	<100
Simmonds *et al.*, 1974 (CCl_3F)		110		Aver. 650			260

VIII. CHEMISTRY

A. Reactions Involved in Use

With the exception of their use as chemical intermediates, the fluorocarbon compounds being reviewed find applications due to their chemical stability rather than chemical reactivity. This chemical stability is a result of the strength of the C-F bond and the increase in the bond energy of the C-Cl bond as the fluorine substitution increases. This is illustrated in Table XXII.

Table XXII: Bond Energies of Chlorofluorocarbons (Kcal/mole)(Bower, 1973)

Compound	C-C	C-Cl	C-F
CCl_4	-	69	-
CCl_3F	-	74	99
CCl_2F_2	-	81	107
$CClF_3$	-	85	114
CF_4	-	-	122
C_2Cl_6	63	68	-
C_2Cl_5F	67	69 73	97
$C_2Cl_4F_2$	72	74	99
$C_2Cl_3F_3$	77	75 79	106
$C_2Cl_2F_4$	83	80	100 108
C_2ClF_5	88	81	109 115
C_2F_6	94	-	116

The hydrolytic and thermal stability, which will be discussed in the following sections, closely parallels these bond energies.

Although quite inert, the fluorocarbons do exhibit some chemical reactivity in various applications. Corrosion of aerosol cans due to the decomposition of the propellants is commonly studied. For example, trichlorofluoromethane is considered unsuitable for water-based products packaged in metal containers since some metals may catalyze the hydrolysis of trichlorofluoromethane with liberation of acid. Sanders (1960) has demonstrated a free-radical reaction between trichlorofluoromethane and alcohols resulting in dichloromonofluoromethane and small amounts of tetrachlorodifluoroethane. The reaction is inhibited by high concentrations of oxygen and, therefore, it is not likely that it will occur in nature. Similar corrosion studies of fluorocarbons 11 and 12 in aerosol cans have been reported (Bohac, 1968; Minford, 1964).

Most common construction metals can be used with the fluorocarbons at normal temperatures although at elevated temperatures they may act as catalysts for the breakdown of compounds. The general order of thermal reactivity with metals is: Least decomposition - Inconol < 18-8 stainless steel < nickel < 1340 steel < aluminum < copper < bronze < brass < silver - Most decomposition. The order of reactivity may vary somewhat with individual compounds. Magnesium alloys and aluminum containing more than 2 percent magnesium are not recommended for use with the fluorocarbons where water may be present (DuPont, 1969a).

Some of the fluorocarbons under review are used to synthesize ethylene monomers which are used in the synthesis of fluorocarbon resins and elastomers. The most important process commercially is the pyrolytic dimerization of chlorodifluoromethane to form tetrafluoroethylene:

$$2CHClF_2 \xrightarrow{500 - 1000°C} CF_2 = CF_2 + 2HCl.$$

The perhalogenated ethanes can be dehalogenated by zinc (also magnesium and aluminum) in the presence of polar solvents:

$$CCl_2F - CClF_2 \xrightarrow[\text{Alcohol}]{Zn} CClF = CF_2 + ZnCl_2$$

B. Hydrolysis

The hydrolysis of the fluorocarbons has received a great deal of study due to its economic importance in the Hydrate Process for desalination (Colten _et_ _al_., 1972; Stepakoff and Modica, 1973; Johnson _et_ _al_., 1972). The hydrolysis reaction is considered to be a first order reaction with the rate determining step being the slow ionization of the fluorocarbon to a carbonium ion and halide ion followed by a faster reaction of the carbonium ion with water (Johnson _et_ _al_., 1972), as depicted for fluorocarbon 31 in Figure 7.

$$CH_2ClF \xrightarrow{1} CH_2F^+ + Cl^- \text{ (slow)}$$
$$CH_2F^+ + H_2O \xrightarrow{2} CH_2FOH + H^+ \text{ (fast)}$$
$$CH_2FOH \xrightarrow{3} HCHO + HF \text{ (faster than 1)}$$

Figure 7: Hydrolysis Mechanism of Fluorocarbon 31 (Johnson _et_ _al_., 1972)

The carbon-chlorine bond is probably the first bond broken in the hydrolysis. Experiments with 1-chloro-3-fluoropropane indicate the rate of hydrolysis of the carbon-chlorine bond is 100 times faster than the carbon-fluorine bond (Bower, 1973).

The fluorocarbons as a group exhibit a low rate of hydrolysis in comparison to other halogenated compounds. Table XXIII presents some rates of hydrolysis in water. When water alone is used, the rate is too low to be determined by the analytical method. Johnson and coworkers (1972) have reported a half-life of 1.2×10^6 hr at 1 atm and 25°C for the hydrolysis of fluorocarbon 114 based on the first order model. The rate of hydrolysis is greatly affected by temperature and pressure and the presence of other materials. For example, metals have a tendency to catalyze the hydrolysis

Table XXIII: Hydrolysis Rate in Water[#]
Grams/(liter of Water)(year)
(DuPont, 1969, no date b)

Compound	1 atm Pressure 86°F		Saturation Pressure 122°F	1% Na_2CO_3 Solution	10% NaOH Solution
	Water Alone	With Steel	With Steel		
CH_3Cl	*	*	110		
CH_2Cl_2	*	*	55		
"Freon" 113	<0.005	ca. 50**	40		
"Freon" 11	<0.005	ca. 10**	28	0.12	100
"Freon" 12	<0.005	0.8	10	0.04	40
"Freon" 21	<0.01	5.2	9		
"Freon" 114	<0.005	1.4	3	0.01	3
"Freon" 22	<0.01	0.1	*	0.6***	955***
"Freon" 502	<0.01†	<0.1†			

#Grams of refrigerant hydrolyzed per liter of solution saturated with gas
*Not Measured
**Observed rates vary
***grams/liter/day
†Estimated

reaction. The pH of the water also has an effect on the rate of hydrolysis of fluorocarbons containing hydrogen (e.g., fluorocarbon 22). Under alkaline conditions, these compounds tend to hydrolyze more rapidly than under neutral or acidic conditions. The results depicted in Table XXIII generally indicate the retarding effect of fluorine substitution on the hydrolysis rate. This has also been demonstrated on a series of chloromethanes (CH_3Cl, CH_2FCl, CHF_2Cl) by Boggs and Mosher (1960).

On theoretical grounds (bond strength of C-Br bond), bromotrifluoromethane should hydrolyze more rapidly than the chlorofluorocarbons. However, Saltzman *et al*. (1966) found no detectable loss of the compound in moist air mixtures which were aged for several days, but this may be attributed to the lack of sensitivity of the technique used.

C. Oxidation

The fluorocarbon compounds are highly resistant to attack by conventional oxidizing agents at temperatures below 200°C (Bower, 1973; Downing, 1966). At elevated temperatures, air contamination can increase the decomposition rates by 300 percent or more (Callighan, 1971).

D. Thermal Stability

In general, the fluorocarbons exhibit a high degree of thermal stability. As noted earlier, the degree of stability is dependent upon the degree of fluorine substitution (see discussion on bond energies in section VIII A). The stability of the compounds is dependent upon the test conditions used and the materials to which the compound is exposed.

Table XXIV: Thermal Stability of Fluorocarbon Compounds (DuPont, 1969a)

Compound	Formula	Maximum Temperature for Continuous Exposure in the Presence of Oil, Steel and Copper, °F	Decomposition Rate at 400°F in Steel, Per Cent/Year	Temperature for First Trace of Decomposition in Quartz, °F
11	CCl_3F	225	2	840
113	$CCl_2F\text{-}CClF_2$	225	6	570
12	CCl_2F_2	250	<1	1000
114	$CClF_2\text{-}CClF_2$	250	1	*
22	$CHClF_2$	300	*	550
502	$CHClF_2/CClF_2CF_3$	300	*	*
13	$CClF_3$	>300	*	*

*Not measured

Table XXIV presents some thermal stability data. The recommended maximum temperatures are based on laboratory tests, but have been in substantial agreement with field experience. The decomposition rates are determined from six-day exposures.

Callighan (1971) has reviewed the available thermal stability data on fluorocarbons 11, 12, 22, 113, 114, and 116 and converted the various test results into "standard" percent per year values. The results can vary considerably depending upon the contaminants (e.g., water and air), exposure time, and whether the experiment was run long enough to reach a steady state. With this in mind, the following approximate decomposition rates were tabulated.

Table XXV: Decomposition Values of Fluorocarbons at 400°F (Callighan, 1971)

	Percent Per Year in Presence of			
	Fe Only		Fe + Cu + Al + oil (naphthenic)	
Fluorocarbon	Lower Limit	Upper Limit	Lower Limit	Upper Limit
114	0.055	1.0	9	22
113	0.2	6	700	710,000
11	2.0	60	too high to estimate	
22	0.1	9.0	0.35	9
12	0.3	1.0	3500	7,100,000
stability rank	114	114	22	22
highest	22	12	114	114
	113	113	113	113
	12	22	12	12
lowest	11	11	11	11

In general, these results agree well with the fluorine substitution pattern. The pyrolysis products usually include hydrofluoric and hydrochloric acid and, if a source of water or oxygen is available, a small amount of phosgene. Thermal dehydrohalogenation can occur with appropriate chlorofluoroethanes to yield substituted ethylenes (Haskins et al., 1951).

E. Photochemistry

Sandorfy and coworkers (Doucet et al., 1973) have examined the vacuum ultraviolet spectra of a series of methane fluorocarbons (13, 13B1, 22, 31, 21, 12 and 11) and have observed no absorption above 200 nm for the chlorofluorocarbons. They have also completed studies with the ethane series (fluorocarbon 113, 114 and 115) and these also exhibit no absorption above 200 nm (Doucet et al., 1974). Since the wavelength of sunlight at altitudes below approximately 50 kilometers falls above 280 nm, there is no mechanism for direct photoalteration of these chemicals in the lower atmosphere. Experimental results under atmospheric conditions uphold this postulated lack of photochemical reactivity. Japar et al. (1974) found no evidence of reaction with fluorocarbons 11, 12, 22, 113, 114, 115 during irradiations ($\lambda > 310$ nm) of mixtures of the fluorocarbons with olefins and nitrogen oxides in a long path infrared cell reaction vessel. Hester et al. (1973) placed fluorocarbons 11 and 12 in ambient air samples and photolyzed them in a 20 liter pyrex carboy with 11 blacklight fluorescent lights for a period of almost 2 months. No change was detected. Also, Saltzman et al. (1966) found no photochemical reactivity for bromotrifluoromethane (13B1) from irradiation with fluorescent black lights.

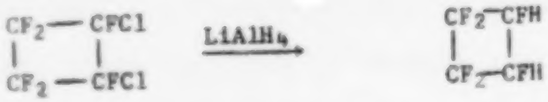
Photolysis of the fluorocarbons at altitudes above 50 kilometers, where the high energy sunlight is not filtered out by the ozone layer, may be a major decomposition route for the removal of the fluorocarbons from the atmosphere. Doucet _et_ _al_. (1973) suggests that the photochemical reactivity at these high energies should increase in the series $CF_3Cl \rightarrow CF_2HCl \rightarrow CFH_2Cl \rightarrow CH_3Cl$ and the same is expected when the number of chlorine atoms is increased or a chlorine is replaced with a bromine.

F. Other Chemical Reactions

The carbon-fluorine bond is extremely resistant to almost all chemical reagents. Reduction with hydrogen does not occur until above 830°C and often the C-C bond is also cleaved

$$C_6F_{12} + H_2 \xrightarrow[>830°C]{} CF_2H_2$$

Strong reducing agents such as lithium aluminum hydride will reduce other halogens but not the C-F bond



In contrast, trifluoromethyliodide will undergo a free radical type reduction simply in the presence of a hydrogen donor (Bower, 1973).

$$CF_3I + C_6H_{14} \longrightarrow CF_3H + C_6H_{13}I$$

The fully halogenated chlorofluorocarbons are inert to halogenation, but unsaturated compounds and the compounds containing a hydrogen will add or substitute a halogen relatively easily (Bower, 1973).

$$CF_2 = CF_2 + Br_2 \longrightarrow CF_2Br-CF_2Br$$

$$CF_3H + Br_2 \longrightarrow CF_3Br + HBr$$

The fluorocarbons also will react violently with alkali and alkaline earth metals such as sodium, potassium, and barium.

IX. BIOLOGY

A. Absorption/Elimination

Under normal conditions, the fluorocarbon propellants, solvents, and fire extinguishing agents have three routes of entry into terrestrial vertebrates: inhalation, ingestion, and dermal absorption. However, because of the physical properties and uses of these compounds, inhalation is by far the most common route of entry and elimination.

Many of these fluorocarbons have been extensively tested on both standard laboratory mammals and man to determine their absorption and elimination patterns during and after exposure. Generally, two types of exposure have been used: inhalation of air containing a known concentration of fluorocarbons (usually expressed as per cent by volume) and direct inhalation of propellants from bronchodilator-type nebulizers (usually expressed as mg. of fluorocarbon inhaled). For the most part, two techniques have been used for determining fluorocarbon retention: measurement of fluorocarbon blood levels and measurement of fluorocarbons in expired air. Of these techniques, blood levels have been the more used because, in dealing with fluorocarbon exposure, it is often desirable to know or be able to predict the blood levels which will be reached under a given set of conditions - e.g. concentration, duration, activity, species, etc. However, the amount and rate of any gas absorbed and/or eliminated during respiration will depend on a variety of factors such as the physical and chemical properties of the gas, concentration of the gas in inspired air, the breathing patterns of the animal, the size and surface characteristics of the absorbing surface, and the characteristics of the absorbing elements (e.g. blood cells and plasma).

Consequently, blood levels of a gas under similar conditions of exposure may vary with the species, individuals in the species, and a given individual at different activity levels. Further, absorption and elimination are dynamic processes involving equilibria states between the ambient air and blood, between the blood and body tissues, and between the various body tissues themselves. Thus, fluorocarbon absorption data are often given as peak blood levels for a given concentration x time exposure. For those concerned with long term exposures, these values are most instructive when equilibria is reached. Elimination data is similarly given as half-life, time to total or partial elimination, or percent elimination at a given time measured either as blood levels or percent eliminated in expired air.

Although the various types of information available on fluorocarbon absorption are not contradictory, they are nonetheless difficult to compare, either because of the units in which they are expressed or the experimental conditions under which they are obtained. Therefore, three types of information will be considered separately: 1) information derived on fluorocarbon retention from concentrations in expired air; 2) fluorocarbon blood levels after inhalation from nebulizer apparatus; and 3) fluorocarbon blood levels after inhalation of fluorocarbon-containing ambient air.

1. Fluorocarbons in Expired Air

The relative amounts of fluorocarbons F-11, F-12, F-113, and F-114 absorbed by man have been measured in breath holding experiments (Morgan et al., 1972). Such experiments involve having the subject inhale a known concentration of a ^{38}Cl-labelled fluorocarbon, then measuring the activity in alveolar air after varying periods of breath holding. The results are given in Figure 8.

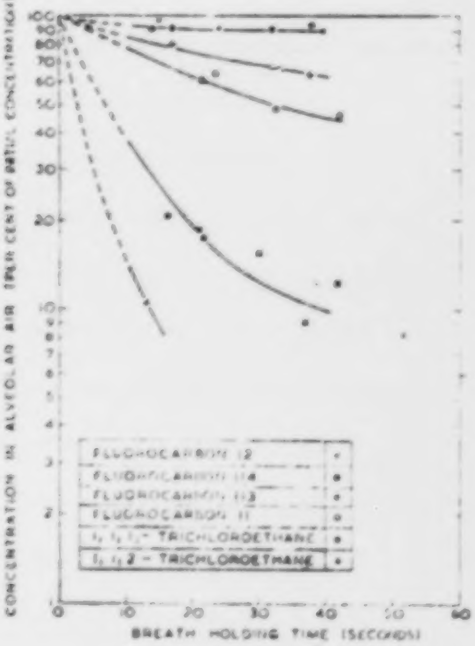


Figure 8: Concentrations of Some Halogenated Hydrocarbons in the Alveolar Air of Man after Varying Periods of Breath-holding (Morgan et al., 1972) Reprinted with permission from A. Morgan, Copyright 1972, Pergamon Press.

Qualitatively, these results agree well with other information on the amount of fluorocarbons absorbed by the blood indicating the following order: F-11>F-113>F-114 F-12. As pointed out by the various investigators referenced in Table XXVI, this order agrees well with the blood/gas partition coefficients for these compounds in blood, blood serum, and olive oil.

Table XXVI: Partition Coefficients of Various Fluorocarbons

Compound	Whole blood (rat)[1]	Whole blood (man)[2]	Blood serum (man)[3]	Olive Oil[3]
F-11	1.4	0.87	0.9	27
F-12	0.2	0.15	0.2	3
F-113			0.8	32
F-114		0.15	0.2	5

[1] Allen and Hanburys Ltd., 1971
[2] Chiou and Niazi, 1973
[3] Morgan et al., 1972

The values for olive oil compare reasonably well enough to those of blood so that they might be indicative of blood/gas partition coefficients for fluorocarbons. Halothane (1-bromo-1-chloro-2,2,2-trifluoroethane), a potent anesthetic, has a partition coefficient in human blood of 2.3 (Larson, 1962). The blood gas partition coefficients for 1,1,1-trichloroethane and 1,1,2-trichloroethane (see Figure 8) are 7 and 56 respectively, indicating that correlation of blood/gas partition coefficient to absorption may hold for all volatile halocarbons. When exposure is terminated and equilibria forces are reversed, the more readily absorbed compounds are retained longer. This is demonstrated in Figure 9 for F-11 and F-12.

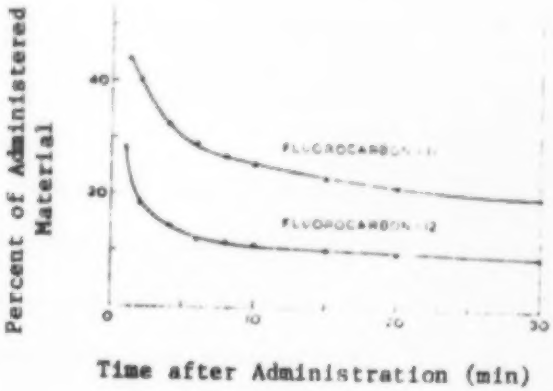


Figure 9. Retention Times of Halogenated Hydrocarbons Following Single Breath Administration in Man (Morgan et al., 1972)
Reprinted with permission from A. Morgan, Copyright 1972, Pergamon Press.

The inverse relationship between ease of elimination and absorption is further illustrated by data on percent retention after 30 minutes and the number of respiratory cycles to total elimination as given in Table XXVII.

Table XXVII. Elimination of Fluorocarbons as Measured in Expired Air

Fluorocarbon	% Retained after 30 Minutes[1] Mean (S.D.)	Number of Respiratory Cycles to 100% Elimination[2]
F-11	23.0 ± 2.2	127
F-12	10.3 ± 2.2	41
F-113	19.8 ± 0.9	-
F-114	12.3 ± 4.1	39

[1] Morgan _et_ _al_., 1972
[2] Paulet and Chevrier, 1969

Additional data by Paulet and coworkers (1969) indicate that the differences between F-12 and F-114 are insignificant. Thus, the retention of fluorocarbons after inhalation follows the same order as the amount absorbed during exposure: F-11>F-113>F-114=F-12.

The above exposures, while useful in determining relative rates of absorption and elimination, are obtained over relatively short periods of time and offer little information on long term exposure. Reinhardt and coworkers (1971b) have conducted retention experiments on F-113 in man over occupationally relevant periods. They measured the retention of F-113 as indicated by fluorocarbon concentration in expired air from human volunteers exposed to 0.05% and 0.1% F-113. Exposure periods were three hours in the morning and three hours in the afternoon. Breath samples were taken before the morning exposure (A.M. data) and after the afternoon exposure (P.M. data). The results are given in Table XXVIII.

Table XXVIII. Concentration of F-113 in Alveolar Air (ppm) After Exposure to 0.05% and 0.1% F-113 (Reinhardt et al., 1971b).

		Exposure				Post Exposure
		500 ppm		1000 ppm		
Subject	Day of Week	a.m.	p.m.	a.m.	p.m.	a.m.
I	M	< 1	60	< 1	113	< 1
	T	< 1	65	< 1	88	< 1
	W	< 1	59	2.0	71	--
	T	< 1	57	1.5	105	--
	F	< 1	51	1.5	93	--
II	M	< 1	61	< 1	115	1.5
	T	< 1	56	1.5	85	< 1
	W	2.0	51	1.5	102	--
	T	< 1	49	1.0	79	--
	F	< 1	55	1.5	103	--
III	M	< 1	45	< 1	88	< 1
	T	< 1	27	< 1	66	< 1
	W	1.5	18	2.0	57	--
	T	< 1	18	3.0	54	--
	F	3.0	31	1.0	60	--
IV	M	< 1	47	< 1	84	< 1
	T	< 1	44	1.0	67	< 1
	W	< 1	35	1.5	56	--
	T	1.0	35	2.0	60	--
	F	< 1	41	2.0	71	--

Note: (--) Indicates not measured.

Although there is no indication of fluorocarbon accumulation, detectable levels were retained over night in four cases at 0.05% and in fourteen cases at 0.1% exposure levels. In one instance, a detectable level was found on the Monday morning after a two day weekend following the final exposure to 0.1%

F-113 (Reinhardt et al., 1971). This information would seem at least an indirect indication of tissue storage requiring a "wash out" period of over 60 hours.

2. Fluorocarbon Blood Levels After Nebulizer Administration

Studies of the amount of fluorocarbons in the blood have concentrated on two types of exposures, those resulting from inhalation of air with known concentrations of the gases and those from direct inhalation of propellants from bronchodilator-type nebulizers. The analytical techniques used in these experiments - headspace, direct injection, and solvent extraction - are discussed elsewhere (Terrill, 1972a and b; Chiou and Niazi, 1973).

Bronchodilator drugs, such as isoproterenol are frequently provided in nebulizers and propelled by various fluorocarbons. With each depression of the value or puff, a fixed amount of drug and fluorocarbon mixture is released. Some of these drugs and the amounts of various fluorocarbons released with each puff are given in Table XXIX.

Table XXIX. Some Bronchodilator Drugs and the amount of Fluorocarbons used as Propellants (Patterson *et al.*, 1971).

Fluorocarbon	Fluorocarbon content (mg.) per puff of:					
	'Medihaler Iso' (isoprenaline)	'Medihaler Iso-forte' (isoprenaline)	'Alupent' (orciprenaline)	'Isomist' (isoprenaline)	'Ventolin' (salbutamol)	'Th1165a'*
11	8.57	8.62	15.30	28.0	25.0	28.7
12	17.14	16.55	35.92	60.0	65.0	61.0
113	0.35	0.35	2.45	..	..	..
114	8.57	8.27	15.30	..	..	..

* Contains 1-(3,5-dihydroxyphenyl)-1-hydroxy-2-1-(4-hydroxyphenyl)-isopropylaminoethane.

These are given only as examples and may not reflect the precise amounts currently used. Typically, in experiments used to determine blood levels from such administrations, various mixtures of propellants are used. At present, there is no definite indication that the presence of one propellant influences the relative degree of absorption of another propellant. This is demonstrated in the work of Shargrel and Koss (1972) who have exposed dogs to an equal weight mixture of F-11, F-12, F-113, and F-114. The dogs were given five and ten doses containing 16.8 mg of each fluorocarbon per dose. The peak arterial and venous blood levels are given in Table XXX.

Table XXX. Peak arterial and Venous Blood Levels of Fluorocarbons in dogs (Shargrel and Koss, 1972)

Fluorocarbon	Peak Level, ug ./ml. 10 Actuations	Peak Level, ug ./ml. 5 Actuations	Peak Arterial Level as Percent of Administered Dose 10 Actuations	Peak Arterial Level as Percent of Administered Dose 5 Actuations
F-11				
Arterial	22.3 ± 1.0	13.2 ± 1.4	15.9	8.89
Venous	6.22 ± 2.6	2.45 ± 0.29		
F-12				
Arterial	6.17 ± 0.38	3.16 ± 0.06	4.41	4.51
Venous	1.54 ± 0.84	0.56 ± 0.04		
F-113				
Arterial	11.56 ± 1.78	6.43 ± 0.61	8.26	9.19
Venous	2.96 ± 1.40	0.79 ± 0.06		
F-114				
Arterial	3.80 ± 0.52	2.32 ± 0.12	2.71	3.31
Venous	0.87 ± 0.41	0.26 ± 0		

These results are in agreement with the order of fluorocarbon absorption given previously: F-11>F-113>F-12=F-114. Considering only the above data, it is tempting to speculate that the order generally follows the blood/gas partition coefficients, with the smaller molecules being more readily absorbed in cases where partition coefficients are approximately equal. Data presented in Part 3 of this section seems to support this assumption (see page 85). Special note should be taken of the sharp drop in arterial/venous ratios seen in all of these fluorocarbons indicating tissue absorption. These data along with other detailed kinetic studies of the arterial/venous drop are discussed in the latter part of this section (see page 90 ff.).

Further absorption and elimination data are available in F-11 and F-12 for nebulizer administration and are summarized in Table XXXI followed by a discussion of the more significant results.

Dollery and coworkers (1970) measured the venous concentration of F-11 in two human volunteers inhaling discharges from a nebulizer administering F-11, F-12, and F-114 at 8.6 mg, 17.2 mg, and 8.6 mg per dose, respectively. Volunteer A inhaled ten doses for a total F-11 exposure of 86 mg and volunteer B inhaled thirty doses for a total F-11 exposure of 258 mg, resulting in peak venous blood concentrations of 0.3 μg/ml and 1.10 ug/ml, respectively. Concentration-time plots for these two exposures are given in Figure 10.

Table XXXI: Absorption/Elimination Data in Various Mammalian Species After Inhalation of F-11 and F-12 from Nebulizers

Fluorocarbon (Code)	Animal	Exposure		Absorption			Amount Eliminated (%) or Venous Blood Levels (µg/ml)	Time to Elimination (minutes)	Comments	Reference
		mg/puff x no. of puffs	Dosage Inhaled	Peak Blood Levels (µg/ml) Arterial	Venous	Half Life (minutes)				
CCl_3F (F-11)	Human	8.6 x 10 8.6 x 30 8.6 x 3	86 mg 285 mg 25.8 mg	 1.7	0.3 1.10				see Fig. 10	Dollery et al. 1970
	Human (U.L.L.)	8.6 x 6	51.6 mg	1.63						
	Humans	25 x 2	50 mg		0.68 (30 sec)# 0.27 (75 sec)# 0.29 (90 sec)# 1.60 (30 sec)# 0.52 (69 sec)#	0.1 1.0 1.5 0.1 0.9			see Fig. 11	Patterson et al. 1971
	Humans	25.5 x 10	255 mg		0.93 (0.51-1.20)		1.32 (1.15-3.47)	9	with F-12, see Table XXXII	Allen & Hanburys Ltd., 1971
	Dogs	75 x 75	1800 mg		60-75	0.6 ± 0.12 initial 4.03 ± 0.13 terminal 3			with F-12	McClure, 1972
	Dogs (S)	24 x 22-30	528-720 mg		22.8-75				with F-12	Allen & Hanburys, Ltd., 1971
	Dogs (S)	24 x 25	600 mg		29.6-88.1				with F-12	
	Dogs	16.8 x 5 16.8 x 10	84 mg. 168 mg.	13.2 ± 1.6 23.3 ± 1.0	2.65 ± 0.28 6.22 ± 2.6				see Table XXX with F-12, F-113, and F-114	Shargel & Koss, 1972
	Mice* (L)	24 mg/puff			6.97 (2.80-11.60)		4.13 (3.20-5.83)	15	see Table XXXIII with F-12	Allen & Hanburys, Ltd., 1971
	Mice*	24 mg/puff			11.33 (8.0-20.3)		1.36 (1.0-2.0)		with F-12	
CCl_2F_2 (F-12)	Humans	66.5 x 10	665 mg		2.17 (1.40-2.70)		7.4	9	with F-11 see Table XXXII	Allen & Hanburys, Ltd., 1971
	Dogs (S)	61 x 22-30	1342-1830 mg.		12.5-110.0				with F-11	Allen & Hanburys, 1971
	Dogs	16.8 x 5 16.8 x 5	84 mg 168 mg	3.16 ± 3.08 6.17 ± 0.38	0.56 ± 0.06 1.14 ± 0.84				see Table XXX with F-11, F-113, and F-114	Shargel & Koss, 1972
	Mice*	61 mg/puff			32.1 (10.2-56.6)				see Table XXXIII with F-11	Allen & Hanburys, Ltd., 1971

* = anesthetized
(S) = under stress
(L.L.) [illegible] lungs

Subjects were [illegible] to screen out particular [illegible]
from [illegible] as in Taylor and [illegible]
= time to peak
x inhalations

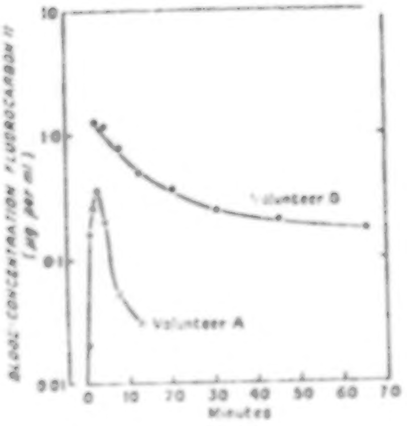


Figure 10. Venous Blood Concentrations of human inhaling 86 mg F-11 (Volunteer A) and 258 mg F-11 (Volunteer B) from a nebulizer (Dollery et al., 1970).
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However, in a different individual a dose of only 50 mg F-11 resulted in a peak venous blood concentration of 0.52 µg/ml as indicated in Figure 11.

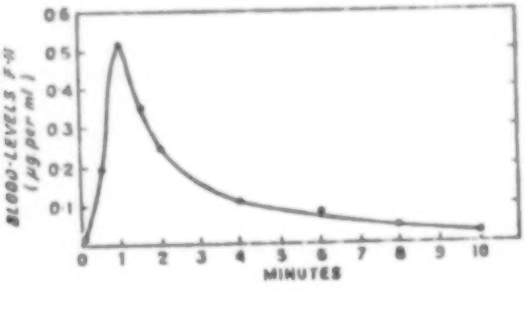

Figure 11. Venous Blood Concentrations of F-11 in a Human Inhaling 50 mg F-11 (Patterson et al., 1971).
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While the general patterns of the preceding figures are quite similar, showing the same rapid initial rise in blood levels with dosing followed by an initially rapid then slower decline in blood levels when exposure is terminated, there is some evidence that the amount of fluorocarbons absorbed may vary considerably among different individuals. Dollery and coworkers (1970) noted that a healthy individual inhaling 25.8 mg F-11 reached a maximum arterial blood level of 1.7 μg/ml F-11, while a patient with obstructed lungs inhaling 51.4 mg F-11 reached a maximum arterial blood level of only 0.63 μg/ml F-11. In this instance, the difference is probably attributable to diminished lung capacity in the patient inhaling the higher dose. Patterson and coworkers (1971) noted a ten-fold difference in peak venous blood concentrations and a five-fold difference in F-11 blood half lives among five patients inhaling 50 mg F-11 (see Table XXXI). This variation could not be explained by differences in lung capacity. However, an inverse correlation is noted between the venous peaks and the half-lives, indicating that wide variations noted reflect different inhalation techniques - e.g. the individual breathing most deeply reached the highest blood level (2.60 μg/ml) most quickly (30 seconds) and eliminated the fluorocarbon most rapidly ($t_{½}$ = 18 seconds), with the converse being seen in the patients breathing most shallowly: peaks of 0.27 and 0.29 μg/ml, time to peaks of 75 and 90 seconds, half lives of 90 and 60 seconds, respectively.

Experiments conducted at Allen and Hansbury Ltd. (1971), noted similar differences in maximum venous concentrations in three humans deeply inhaling or not inhaling ten doses of F-11 (25.5 mg/dose) and F-12 (64.5 mg/dose), one dose every six seconds sprayed into the mouth. The results are given in Table XXXII.

Table XXXII. Concentration of F-11 and F-12 in venous blood of three humans exposed to ten doses of 25.5 mg F-11/dose and 64.5 mg F-12/dose, one dose every six seconds (Allen and Hansbury Ltd., 1971).

Time after exposure (minutes)	μg/mg. Blood					
	Volunteer A		Volunteer B		Volunteer C	
	Arcton 11	Arcton 12	Arcton 11	Arcton 12	Arcton 11	Arcton 12
	Deep Inhalation					
0	0.81	1.60	1.18	2.45	0.31	0.75
1	1.10	2.40	1.20	2.70	0.51	1.40
2	No specimen		0.96	2.00	0.49	1.36
5	0.79	1.50	0.80	1.25	0.39	0.95
10	0.25	0.35	0.47	0.60	0.25	0.50
	No Inhalation					
0	1.62	2.07	0.34	0.47	0.93	1.55
1	0.63	0.80	0.33	0.40	1.24	1.58
2	0.27	0.25	0.26	0.28	1.07	1.07
5	0.20	0.15	0.22	0.20	0.93	0.95
10	0.13	0.08	0.15	0.13	0.64	0.68

The wide differences noted in blood concentrations, especially in volunteers B and C, demonstrate the importance of inhalation technique on the absorption of these fluorocarbons into the blood. The ratio of administered

F-12 to F-11 in the above exposures is 2.58 to 1, while the ratios of maximum levels found in the blood after deep inhalation are 2.18, 2.25, and 2.75 for volunteer A, B, and C, respectively. Thus, F-11 seems to be more readily absorbed than F-12 in volunteers A and B but not in volunteer C. This might be seen as an indication that there is individual variation not only in the amounts of fluorocarbons absorbed but also in relative degrees of absorption. While F-11 is usually considered more readily absorbed than F-12, volunteer C in Table XXXII presents an apparent exception. Further exceptions are apparent with studies on anesthetized mice (Allen and Hanbury Ltd., 1971). In this study, mice were allowed three inhalations from one dose of a Ventolin inhaler. A gauze filter was inserted into the mouth of the nebulizer to screen out the active ingredients. The amount of fluorocarbons in such a dose are 25 mg F-11 and 65 mg F-12 with a weight ratio of F-12 to F-11 of 2.6 (Patterson et al., 1971). The venous blood levels found in these mice are given in Table XXXIII.

Table XXXIII. Venous blood levels of F-11 and F-12 in mice after three inhalations from one dose of a Ventolin inhaler (Allen and Hanbury Ltd., 1971).

Mouse Number	µg./mg. Blood		Ratio F-12/F-11*
	Arcton 11	Arcton 12	
1	9.06	16.2	1.8
2	5.78	47.3	8.2
3	8.26	56.4	6.8
4	2.86	18.9	6.6
5	5.39	26.6	4.9
6	11.48	27.8	2.4

* F-12/F-11 in administered dose equals 2.6.

The ratios above 2.6 might seem to indicate that mice #2-5 absorbed F-12 more readily than F-11. An alternate explanation implied by the original investigators is that the relatively non-volatile F-11 was preferentially absorbed into the gauze and thus the actual dose of F-11 received by the mice was lowered. This is supported by the higher blood levels of F-11 (8.0, 12.0, and 20.2 μg/ml) in mice exposed without gauze.

In a similar series of experiments on hypoxic dogs, using the same ratio of F-12 to F-11 (2.6), F-12/F-11 ratios in venous blood varied from 0.55 to 1.57, indicating preferential absorption of F-11 in all cases but not uniformly so. Thus, this series of studies seems to indicate that while F-11 is more readily absorbed by mammals than F-12, the degree of preferential absorption may vary among individuals. Whether this difference is actual or merely an artifact of the relatively high volatility of F-12 over F-11 has not been conclusively demonstrated.

From the data presented on mice, dogs, and humans exposed to fluorocarbons from bronchodilator-type nebulizers, it would be desirable to determine and quantify interspecific differences. Jack (1971), in discussing the data presented by Allen and Hansbury's Ltd. (1971), concluded that dogs absorb fluorocarbons to a much greater extent than man. For the most part, this conclusion is supported by the data presented in Table XXXI for both F-11 and F-12. However, the wide variety of blood levels after identical exposures (e.g., Patterson et al., 1971) should not be minimized. In one human receiving 50 mg F-11, venous blood levels peaked at 2.60 μg F-11/ml (Patterson et al., 1971). In dogs inhaling 84 mg F-11, venous blood levels peaked at 2.45 ± 0.29 μg F-11/ml (Shargrel and Koss, 1972). Also, dogs have a much smaller respiratory volume than man. Consequently, an equal dose of fluorocarbons is less diluted in the alveolar air resulting in artificially higher blood levels in dogs than in man. Thus, differences in levels of absorption between man and dog might best be demonstrated in exposures to concentrations of fluorocarbons in ambient air rather than direct administration from nebulizers. The data on mice are of little use in determining comparative absorption because the actual doses cannot be fixed. These exposures relate more to experiments on fluorocarbon sensitization to asphyxia induced arrhythmias (see Section XII, Part D-3). Lastly, it is of interest to note that all of the blood levels obtained are well below the level of halothane stage-3 anesthesia, 173 μg/ml (Dollery et al., 1970).

3. Fluorocarbon Blood Levels after Inhalation of Fluorocarbon-containing Ambient Air

Exposures to fluorocarbons at fixed concentrations in inspired air generally reflect the same basic pattern as those seen for nebulizer exposures (see Figures 10 and 11). Changes in venous blood concentrations in dogs during and after exposure to F-11 have been measured at ambient concentrations of 1.25% and 0.65% for 30 minutes (Clark and Tinston, 1972a) and at 0.55% for 20 minutes (Blake and Mergner, 1974). The results of these investigations are given in Figure 12.

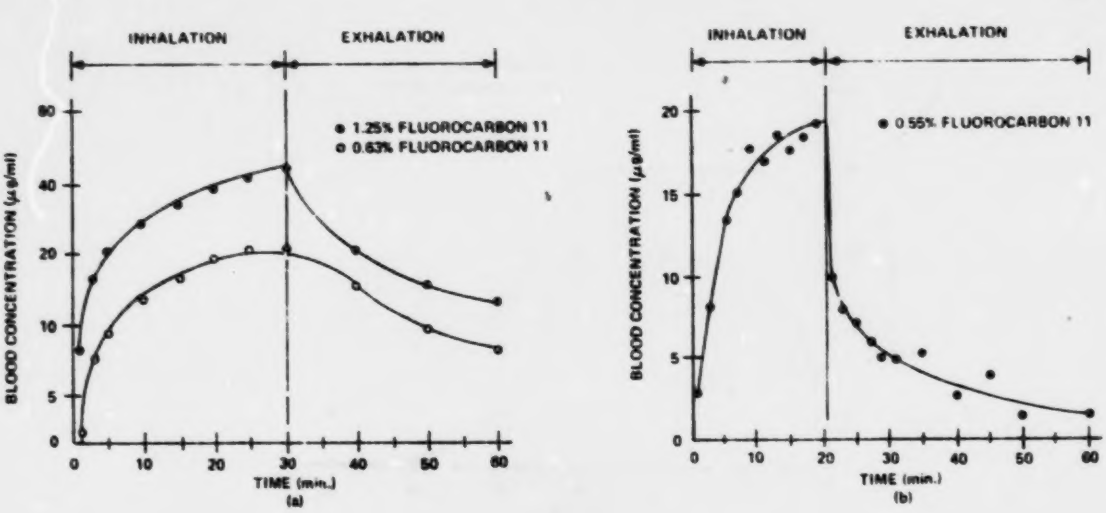


Figure 12. Changes in Venous blood concentrations of F-11 in dogs exposed to (A) 1.25% and 0.63% F-11 for 30 minutes (Clark and Tinston, 1972a) and (B) 0.55% F-11 for 20 minutes (Blake and Mergner, 1974).

Similar studies have been conducted on F-12 and F-114 and are summarized in Figures 13 and 14.

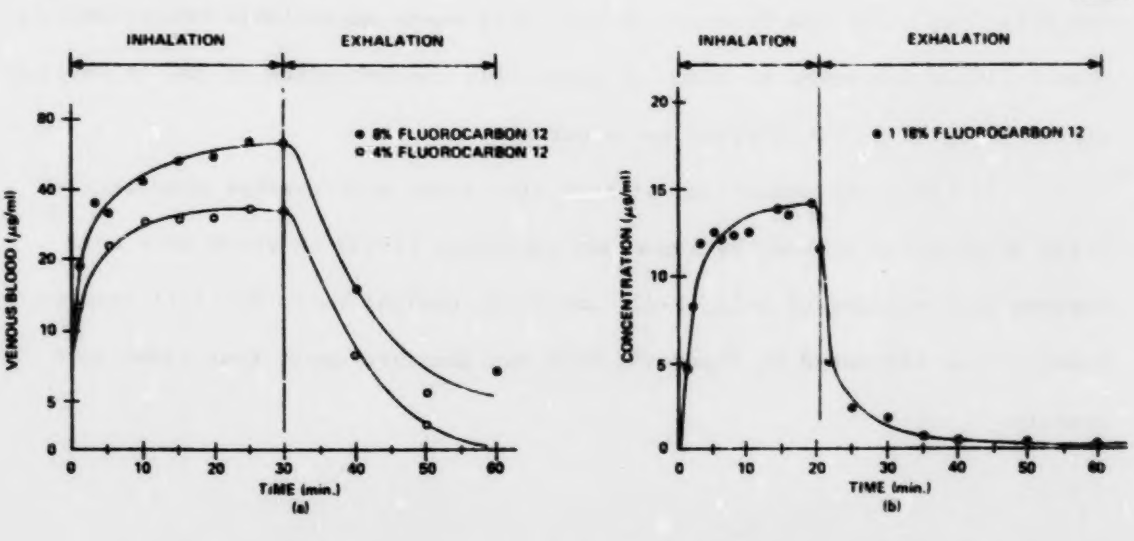


Figure 13. Changes in Venous Blood Concentrations of F-12 in dogs Exposed to (A) 8% and 4% F-12 for 30 minutes (Clark and Tinston, 1972a) and (B) 1.18% for 20 minutes (Blake and Mergner, 1974)

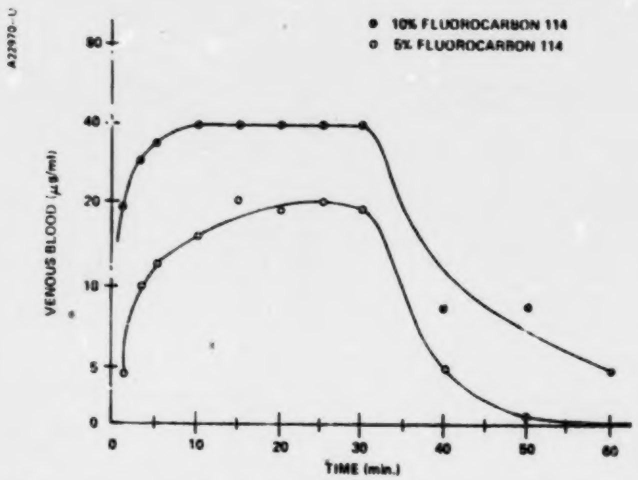


Figure 14. Changes in Venous Blood Concentrations of F-114 in dogs exposed to 10% and 5% F-114 for 30 minutes (Clark and Tinston, 1972a).

As in the studies using expired air or blood levels from nebulized administration as indices of absorption, the above data indicate that F-11 is much more readily absorbed and retained than either F-12 or F-114. However, in the data from Clark and Tinston (1972a), F-12 seems appreciably better absorbed than F-114, which seems to reach an equilibria concentration of 10% in inspired air to 40 µg/ml in blood after ten minutes.

In rats, the absorption of F-12 also seems much greater than that of F-114 as shown in a study by Ramus and coworkers (1973) in which rats were exposed to a mixture of F-11, F-12, and F-114 (weight ratio of 1:2:1 respectively). As indicated in Figure15, F-12 was absorbed about four times more readily.

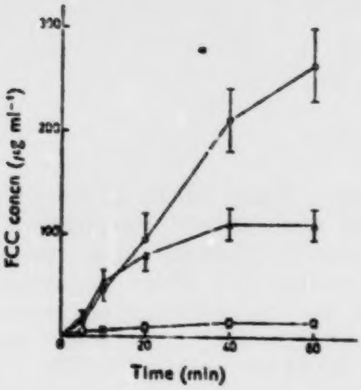


Figure 15. Increase of fluorocarbons (FCC) concentrations in rat blood during inhalation of a combination of FCC's 11 (O), 12 (Δ) and 114 (□) (weight ratio 1:2:1, mean ± s.d., 6 rats).(Rauws, et al., 1973); reprinted with permission from A.G. Rauws, Copyright 1973, Pharmaceutical Society of Great Britain.

A similar pattern is also seen in the work of Taylor and coworkers (1971) who have exposed monkeys to a mixture of 30% F-12 and 9% F-114 (ratio 3.3:1::F-12: F-114) for varying periods. The arterial blood levels monitored are given in Table XXXIV.

Table XXXIV. Arterial blood levels of F-12 and F-114 in monkeys exposed to 30% F-12 and 9% F-114 (3.3:1, v/v; 2.35:1, w/v) [Taylor et al., 1971].

	Arterial Blood Conc. (mg/100 ml.)		
Duration	F-12	F-114	Ratio
35 sec.	5.5	1.8	3.06
42 sec.	6.3	2.3	2.74
45 sec.	6.5	2.2	2.96

In each instance, the ratio of F-12 to F-114 in arterial blood is higher than the w/v ratio of exposure indicating that F-12 is slightly better absorbed than F-114. Thus, as mentioned previously, it seems reasonable to assume that ease of absorption for the fluorocarbon gases follow the blood/gas partition coefficients, with the smaller molecules being more readily absorbed in cases where partition coefficients are approximately equal.

There is also some indication in these exposures of interspecific differences in absorption. Griffin and coworkers (1972) have exposed rabbits to 5% F-12 for thirty-five minutes. The resulting venous blood levels are summarized in Figure 16.

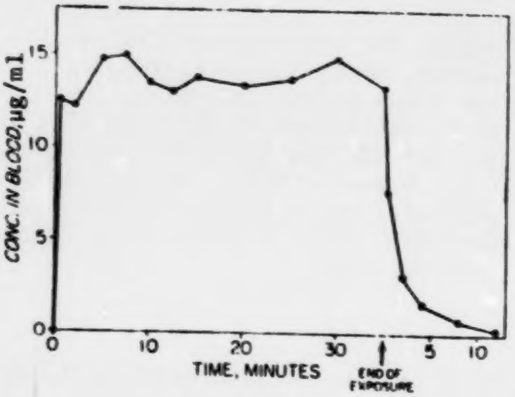


Figure 16. Freon 12 in blood of rabbit during 5% atmospheric exposure. Blood samples were withdrawn from the animals before, during and after exposure to Freon 12 and the halocarbon concentrations determined by gas-liquid chromatography. (Griffin et al., 1972)

The peak blood levels (about 15 µg/ml) are about 5 µg/ml below those noted in dogs exposed to 4% F-12 for 30 minutes (see Figure 13, Clark and Tinston, 1972a), indicating that dogs may absorb F-12 more readily than rabbits.

Information on the absorption of F-116 and H-1301 are also available on rabbits during 30 minute exposures to 5.0% fluorocarbon.

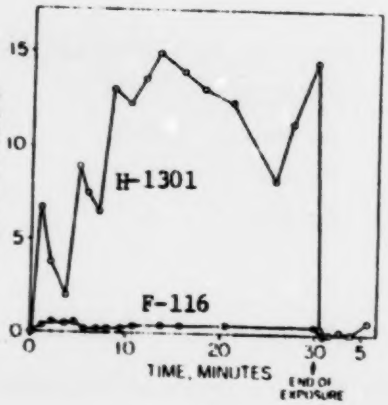


Figure 17. Fluorocarbons in blood of rabbits during 5% atmospheric exposures. Blood samples were withdrawn from the animals before, during and after exposures to either H-1301 (open circles) or F-116 (solid circles). Concentrations of the halocarbons in blood were determined by gas-liquid chromatography (Griffin et al., 1972).

An exposure to 5% H-1301 for 50 minutes resulted in a much lower blood concentration in rats as shown in Table XXXV.

Table XXXV. H-1301 in Rat Blood Following a Single 50-Minute Exposure to a Vapor Concentration of 5% (V/V) (Griffin et al., 1972).

Post-Inhalation Time (Hrs)	Venous Blood Level µg/g
0	5.6
0.25	0.62
1.0	0.35
2.0	0.05
4.0	0.07

This would seem to indicate that rats absorb H-1301 less readily than do rabbits.

Exposure of rats to 3.7% H-2402 for 30 minutes resulted in a much higher blood concentration and correspondingly longer retention times as shown in Table XXXVI, than the comparable exposure to H-1301 shown in Table XXXV.

Table XXXVI. Blood Levels of H-2402 in Rats After a 30-Minute Exposure to 3.7% H-2402 (Griffin *et al.*, 1972).

Post-Inhalation Time (Hrs)	Venous Blood Levels µg/g
0	87
1.5	7
3	0.23
24	0.22

Data on these and other exposures are summarized in Table XXXVII.

All of these exposures show a similar pattern, an initial rapid rise in fluorocarbon blood levels at the onset of exposure followed by a slower rise approaching equilibrium.

In the above cited studies, air-blood equilibrium seems to have been reached with 10% F-114 after ten minutes (Figure 14) and 4% or 5% F-12 after a somewhat longer period (Figure 13 A and Figure 16). However, complete equilibrium would be demonstrated only by knowing both the arterial and venous concentration (see discussion on tissue uptake at end of section). The biphasic rates of absorption are paralleled by elimination rates after termination of exposure. Initially, a sharp drop in fluorocarbon blood levels is seen followed by a much slower fall. The dual rates of elimination have been quantified by McClure (1972), as indicated in Table XXXVII for F-11. These dual rate patterns of absorption and elimination would seem to indiate that these fluorocarbons are deposited from the blood into body tissues during exposure.

Table XXXVII: Absorption/Elimination Data on Various Fluorocarbons after Inhalation

Fluorocarbon (Code)	Animal	Exposure		Absorption		Elimination			Comments	Reference
		Duration of Exposure (minutes)	Concentration in Air (% V/V) or Dosage Inhaled (mg)	Peak Blood Levels (µg/ml)		Half Life	Blood Levels After Exposure (µg/ml)	Blood Level Reduction		
				Arterial	Venous					
$CC\ell F_3$ (F-11)	Rats	5	0.23%		11.25 (11.00-11.70)		0.34 (0.17-0.52)	5 min.		Allen & Hanburys, Ltd., 1971
			0.61%		26.6 (22.3-31.0)		2.35 (2.00-2.70)	5 min.		
	Rats*		0.64%		14.06 (11.25-16.87)		5.97 (55.55-6.40)	5 min.		
	Dogs A	5	0.11%		4.80	3 min.				Allen & Hanburys, Ltd., 1971
	B	5	0.15%		5.80					
	B	5	0.47%		17.50					
	C	5	0.49%		25.40					
	A	5	0.91%		38.00					
	C	5	1.14%		54.00					
	Dog* D	5	0.2%	6.40	3.50				See Table XXXVIII, b.	Allen & Hanburys, Ltd., 1971
	D	5	0.5%	32.25	23.50					
	Dogs	20	0.55%		19.00				See Fig. 12B	Blake & Mergner, 1974
	Dogs	30	0.65%		20.00				See Fig. 12A	Clark & Tinston, 1972a
		30	1.25%		46.00					" " 1972b
	Dogs	5	0.65%		10.00					
		5	1.25%		20.00					
	Dogs	10	0.1%	10.9 (5.6-12.0)	6.6(5.0-9.8)				See Fig. 18	Azar *et al.*, 1973
		10	0.5%	28.6 (13.0-43.5)	19.7 (18.8-24.0)					
		10	1.0%	53.2 (36.0-76.0)	37.2 (31.0-43.0)					

Table XXXVII (continued)

		Exposure		Absorption		Elimination				
Fluorocarbon (Code)	Animal	Duration of Exposure (minutes)	Concentration in Air (% V/V) or Dosage Inhaled (mg)	Peak Blood Levels (µg/ml) Arterial	Peak Blood Levels (µg/ml) Venous	Half Life	Blood Levels After Exposure (µg/ml)	Blood Level Reduction	Comments	Reference
CCl_2F_2 (F-12)	Rats*	5	0.64%		3.47 (2.80-3.75)		0.62 (0.50-0.75)	5		Allen & Hanburys Ltd., 1971
	Rabbit	35 min.	5%		~15				See Fig. 16	Griffin et al., 1972
	Monkey*	0.59	30%	5.5					See Table XXXIV with 9% F-114	Taylor et al., 1971
		0.70	30%	6.3						
		0.75	30%	6.5						
	Dogs A	5	2.40%		25.00					Allen & Hanburys Ltd., 1971
	B	5	2.52%		25.00					
	C	5	2.72%		20.65					
	C	5	4.21%		44.20					
	B	5	4.83%		46.25					
	A	5	5.01%		32.75					
		20	1.18%		~14.5				See Fig. 13B	Blake & Mergner, 1974
		30	4.0%		~33.0				See Fig. 13A	Clark & Tinston, 1972a
		30	8.0%		~65.0				See Fig. 13A	" " "
		10	0.1%	1.2	0.9				See Fig. 19	Azar et al., 1973
		10	5.0%	35.3	22.8					
		10	10.0%	46.3	39.8					
$C_2Cl_2F_4$ (F-114)	Dogs	30	5%		~19.0				See Fig. 14	Clark & Tinston, 1972a
		30	10.0%		40.0					
	Monkeys*	0.59	9%	1.8					See Table XXXIV with F-12	Taylor et al., 1971
		0.70	9%	2.3						
		0.75	9%	2.2						
C_2F_6 (F-116)	Rabbit	30	5%		<0.5				See Fig. 17	Griffin et al., 1972
$CClF_2Br$ (H-1211)	Dog	1	8.0%		21					Beck et al., 1973
		2	5.0%		23					
		5	2.0%		24					
CF_3Br (H-1301)	Rat	50	5.0%		5.6				See Table XXXV	Griffin et al., 1972
	Rabbit	30	5.0%		15.0				See Fig. 17	" "
$C_2F_4Br_2$ (H-2402)	Rats	30	3.7%		87				See Table XXXVI	Griffin et al., 1972

* = anesthetized

Additional indications of body tissue storage comes from simultaneous measurements of fluorocarbon concentration in venous and arterial blood. Such differences have been noted previously in studies by Shargel and Koss (1972) see Table XXX. Similar differences have been noted by Allen and Hansburys Ltd. (1971) and Azar and coworkers (1973). The venous and arterial blood levels during and after exposure of dogs to 0.2% and 0.5% F-11 is summarized in Table XXXVIII.

Table XXXVIII. Arterial and Venous Blood Concentrations of F-11 in Dogs Exposed to 0.2% and 0.5% F-11 (Allen and Hanburys' Ltd., 1971).

Concentration of F-11	Time (minutes)	Time sample taken	μg. F-11/ml. Blood	
			Arterial	Venous
0.2%	0	Start of inhalation	0.12	0.17
0.2%	2.5	After 2.5 minutes	3.63	3.25
0.2%	5	After 5.0 minutes	6.40	3.50
0.2%	10	5 minutes after cessation of inhalation	0.80	0.79
0.2%	15	10 minutes after cessation of inhalation	0.55	0.69
0.2%	20	15 minutes after cessation of inhalation	0.31	0.35
0.2%	25	20 minutes after cessation of inhalation	0.23	0.36
0.5%	0	Start of inhalation	0.08	0.06
0.5%	2.5	After 2.5 minutes	25.15	20.50
0.5%	5	After 5.0 minutes	32.25	23.50
0.5%	10	5 minutes after cessation of inhalation	4.25	5.52
0.5%	15	10 minutes after cessation of inhalation	1.52	3.09
0.5%	20	15 minutes after cessation of inhalation	1.45	1.78
0.5%	25	20 minutes after cessation of inhalation	0.60	0.97

As can be seen in both of the exposures summarized in Table XXXVIII, F-11 is cleared from the blood by tissue absorption during exposure (arterial concentration [Ca]>venous concentration [Cv]) and cleared from tissues by the blood after exposure (Ca<Cv). If equilibria is reached between the inspired air, blood, and body tissues, the values would remain constant. The investigators at Allen and Hanbury's Ltd. (1971) have calculated the rates of both air → blood and blood → tissue uptake after five minutes of exposure to 0.2% and 0.5% concentrations given in Table XXXVIII. The first step is calculated from the following equation:

$$\text{air} \rightarrow \text{blood uptake} = \frac{C_a}{\lambda} \times \bar{V}_a$$

C_a = concentration of fluorocarbon in alveolar air (μg/ml)

V_a = mean minute alveolar ventilation (15 breaths/minute x 120 ml/breath)

$\bar{V}_a = 0.68\ V_a$

λ = blood/gas partition coefficient (see Table XXXVI)

The second step is calculated as:

$$\text{blood} \rightarrow \text{tissue uptake} = \text{cardiac output } (C_a - C_v)$$

The cardiac output of the dog is assumed to be 1 liter/minute. Thus, the rates of air ⟶ blood uptake of F-11 at air concentrations of 0.2% and 0.5% is 5.6 mg/minute and 28.2 mg/minute, respectively; the rates of blood ⟶ tissue uptake are 2 mg/minute and 5.4 mg/minute, respectively.

Azar and coworkers (1973) have monitored both arterial and venous concentrations during and after 10 minute exposures to 0.1%, 0.5%, and 1.0% F-11 and 0.1%, 5.0%, and 10.0% F-12 in dogs. The results are given in Figures 18A and 18B for F-11 and Figures 19A and 19B for F-12.

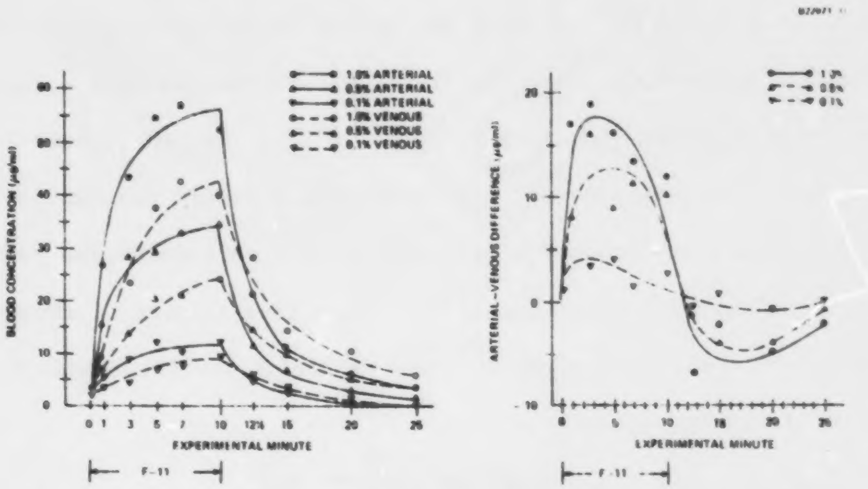


Figure 18. (A) Venous and Arterial Blood Concentrations of F-11 and (B) Arterial and Venous Differences in Dogs exposed to 0.1%, 0.5%, and 1.0% for 10 minutes (Azar et al., 1973).

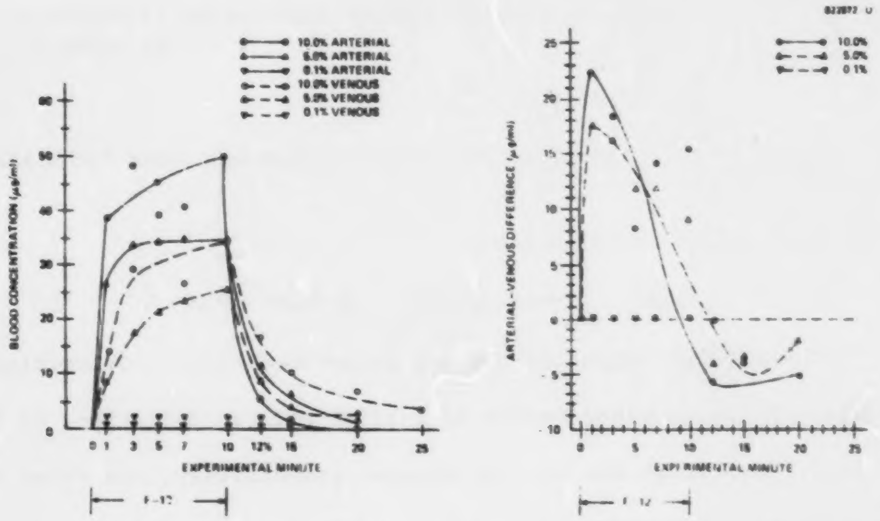


Figure 19. (A) Venous and Arterial Blood Concentrations of F-12 and (B) Arterial and Venous Differences in Dogs Exposed to 0.1%, 5.0%, and 10% F-12 for 10 Minutes (Azar et al., 1973).

The data on the 5.0% exposure to F-12 illustrates the difference between air ↔ blood equilibrium and blood ↔ tissue equilibrium. While the blood levels of F-12 remained constant after 3 minutes indicating an apparent equilibrium between the air and blood, F-12 was still being absorbed by body tissues as indicated by the positive arterial-venous difference. Thus, actual equilibrium - air ↔ blood ↔ tissue - had not yet been attained. When such an equilibrium is attained, the blood levels should remain constant and the arterial-venous difference should equal zero.

4. Other Routes of Entry

Although inhalation is the primary route of entry of the one and two carbon fluorocarbons, other routes of entry have been studied, albeit much less extensively. Greenburg and Lester (1950) found no evidence for the absorption of F-112 or F-112a across the gastrointestinal tract in rats. In long term feeding studies of F-12 to rats and dogs, however, Sherman (1974) found tissue uptake indicating that some absorption does take place. Regardless of the route of entry, fluorocarbon elimination seems restricted almost exclusively to the respiratory tract. Matsumoto and coworkers (1968) have administered a mixture of F-12 and F-114 (30/70, v/v) intravenously, intraperitoneally, and directly sprayed onto an internal organ in dogs. No elimination was noted in the urine or feces. Elimination in the breath is described in Table XXXIX.

Table XXXIX. Elimination of Fluorocarbons in Dogs Breath
(Matsumoto *et al.*, 1968)

	Intravenous	Intraperitoneal	Direct Spray
Dosage	0.5 cc	2.0 cc	--
Internal Before Onset of Elimination	3 sec.	5 min.	5 sec.
Duration of Elimination	12 hours	48 hours	12 hours

The four-fold increase in dosage and the corresponding increase in duration of elimination going from intravenous to intraperitoneal administration would seem to indicate that the half-life of fluorocarbons in the body is relatively independent of route of administration. The increased interval before onset of elimination or intraperitoneal injection probably reflects only the increased time required for the fluorocarbons to enter the circulatory system.

Chiou and Niazi (1973) have conducted similar experiments in the elimination of F-11 in dogs after intraveneous infusion using blood levels rather than fluorocarbon concentrations in expired air as an index in removal. The result of one such experiment is given in Figure 20.

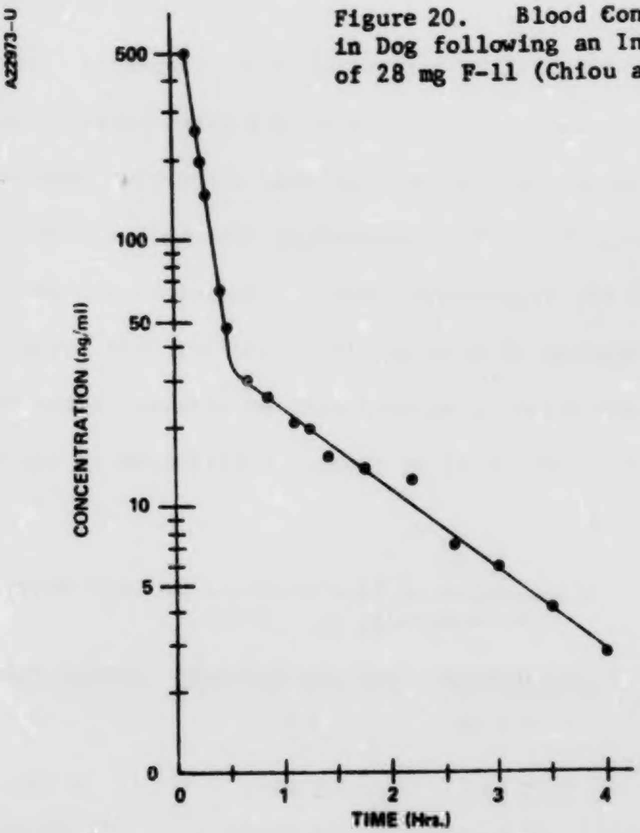


Figure 20. Blood Concentration of F-11 in Dog following an Intravenous Infusion of 28 mg F-11 (Chiou and Niazi, 1973)

The biphasic rates of elimination of F-11 from the blood stream on intravenous infusion are similar to those by inhalation [e.g. Figures 10-14].

Dermal absorption in man has also been tested using F-113 (DuPont, 1968). The hands and arms of two individuals were immersed in F-113 for 30 minutes and the portions of the scalp for 15 minutes. Fluorocarbon uptake was measured as F-113 in expired air. Time to maximum concentration is measured from termination of exposure. The maximum concentrations noted in exposure of the hands and forearms were 9.6 ppm after 11.5 minutes for one individual and 1.7 ppm after 23 minutes for the other. The scalp, perhaps because of its increased vascularity, seems somewhat more absorbent with one individual reaching a maximum fluorocarbon concentration of 12.7 ppm in 20.5 minutes and the other reaching 7.4 ppm after 18.5 minutes. As with the other exposures previously discussed, elimination was rapid. After 90 minutes, F-113 concentration was below 0.5 ppm in all subjects. In the subject reading 1.7 ppm in the hand and forearm exposure, however, a trace amount of about 0.1 ppm was detected 18 hours after exposure.

In summary, the available data on fluorocarbon uptake and elimination indicate that fluorocarbons can be absorbed across the alveolar membranes, gastrointestinal tracts, the skin, or internal organs. On inhalation, fluorocarbons are absorbed rapidly by the blood. As the blood concentration increases, the rate of absorption by the blood decreases. Once in the blood, fluorocarbons are absorbed by various tissues. Current information seems to indicate that blood → tissue absorption is the rate limiting step. If exposure is sufficiently long, blood levels will stabilize indicating an apparent equilibrium between the air and the blood. However, after this initial blood level stabilization, fluorocarbons are still absorbed by body tissue and fluorocarbons continue to enter the body. Actual equilibria - air ↔ blood ↔ tissues - would be indicated by a zero level arterial-venous blood level difference. After exposure, fluorocarbons are eliminated rapidly from the body through the expired air. The relative order of absorption seems to be F-11>F-113>F-12>F-114. Although data on other fluorocarbons are less complete, H-1301 and H-1211 seem to be absorbed to about the same degree as F-12. Halon-2402 is absorbed to a greater extent than F-12 and may approximate F-113 but does not exceed F-11. Fluorocarbon-116 is absorbed very poorly. Differences in the amounts of fluorocarbons absorbed by various species seem evident but are too variable for even a tentative generalized order. Nebulizer administration - while not the preferred technique for demonstrating interspecific differences - seems to indicate that dogs absorb fluorocarbons more readily than man. However, individual differences are most significant, the amounts of fluorocarbon being absorbed or eliminated vary widely and this variety seems chiefly due to variations in breathing patterns.

B. Transport and Distribution

As described in the previous section, kinetic studies on absorption and elimination indicate that fluorocarbons are transported by the blood to the various organs of the body and that some storage - at least temporarily - occurs. This is particularly evident in Table XXXVIII (Allen Hansburys Ltd., 1971) where there is a noticeable decrease in fluorocarbons going from arterial to venous concentrations during exposure but the reverse after exposure is terminated.

Allen and Hansburys Ltd. (1971) have studied the distribution in rats of F-11 and F-12 at varying periods after administration. The results are summarized in Tables XL and XLI.

Based on the kinetic data for F-11 and F-12 blood levels presented in Figures 12 & 13, the tissue concentrations immediately after a five minute exposure to Tables XL and XLI probably do not represent equilibrium concentrations. These studies, however, do indicate that both F-11 and F-12 are taken up by heart, fat, and adrenal tissue. Fluorocarbon-11, for which detailed blood levels are available, is concentrated from the blood to the greatest extent in the adrenals followed by the fat, then the heart. A similar, though less pronounced pattern, is evident for F-12. In agreement with studies presented in the previous section, F-11 is absorbed and concentrated in all of these tissues to a much greater extent than F-12. The differences in actual concentrations noted among the various specimens studied may represent differences in breathing patterns or actual differences in individual ability to absorb these fluorocarbons.

Table XL. Concentration of F-11 in the blood, heart, fat, adrenals, and thymus of rats at various times after exposure to F-11 for 5 minutes (modified from Allen and Hanburys Ltd., 1971)

Animal No.	Concentration Arcton 11 (%)	Time after exposure	µg. F-11				
			Per ml. Blood	Per g. Heart	Per g. Fat	Per g. Adrenals	Per g. Thymus
1	0.23	Immediate	11.00	12.00	83.40	-	-
2	0.23	Immediate	11.70	11.60	61.10	-	-
5	0.61	Immediate	22.30	26.70	113.00	-	-
6	0.61	Immediate	31.00	41.40	164.50	-	-
7*	0.64	Immediate	16.87	21.04	39.60	222.0	-
8*	0.64	Immediate	11.25	21.20	30.85	246.3	-
3	0.23	5 minutes	0.52	0.87	28.60	-	-
4	0.24	5 minutes	0.17	2.47	34.80	-	-
7	0.61	5 minutes	2.70	2.14	77.00	-	-
8	0.61	5 minutes	2.00	4.00	105.70	-	-
9*	0.64	5 minutes	5.55	6.87	16.58	195.4	-
10	0.64	5 minutes	6.40	6.86	17.46	-	-
11	0.64	1 hour	0.32	0.15	2.90	33.75	-
12	0.64	1 hour	0.12	0.28	3.22	45.50	-
1	0.49	2 hours	0.13	0.05	0.64	2.49	-
2	0.49	2 hours	0.09	0.11	2.59	15.88	0
3	0.49	4 hours	0.03	0.03	0.66	2.53	-
4	0.49	4 hours	0.02	0.01	0.15	1.64	-
1	0.64	8 hours	0.007	0.006	1.105	0.347	0.013
2	0.64	8 hours	0.014	0.008	1.850	0.440	0.027
3	0.64	24 hours	0.006	0.011	0.011	0.375	0.025
4	0.64	24 hours	0.006	0.012	0.024	0.305	0.021
1	1.00	48 hours	0.002	0.002	0.011	0.077	0.005
2	1.00	48 hours	0.003	0.005	0.008	0.125	0.007

* Rats anaesthetized with sodium pentobarbitone prior to exposure to F-11/Air mixture

Table XLI. Concentration of F-12 in the heart, fat, and adrenals of rats at various times after exposure to F-12 for 5 minutes (modified from Allen and Hansbury Ltd., 1971)

Animal No.	Concentration Arcton 12 (%)	Time after exposure	µg. F-12		
			per g. Heart	per g. Fat	per g. Adrenals
9	0.18	Immediate	4.17	6.05	78.60
10	0.18	Immediate	4.51	5.08	89.10
5	0.68	Immediate	11.10	11.50	101.00
6	0.68	Immediate	11.10	8.98	70.50
1	0.70	Immediate	7.58	9.93	33.10
2	0.70	Immediate	4.91	4.57	76.60
1*	0.64	Immediate	1.91	5.96	45.80
2*	0.64	Immediate	2.08	4.04	45.10
11	0.18	5 minutes	0.77	1.73	32.10
12	0.18	5 minutes	0.64	1.62	9.50
7	0.68	5 minutes	1.93	2.10	54.50
8	0.68	5 minutes	1.66	1.74	48.00
3	0.70	5 minutes	3.94	3.03	18.25
4	0.70	5 minutes	3.50	0.91	15.60
3*	0.64	5 minutes	0.92	3.91	16.55
4*	0.64	5 minutes	0.82	3.00	22.84
5	0.64	1 hour	0.13	0.07	1.00
6	0.64	1 hour	0.11	0.06	1.04

* Rats anaesthetized with sodium pentobarbitone prior to exposure to F-12/air mixture.

Carter (1970) summarizes similar distribution data on F-113 exposure in rats given in Table XLII.

Table XLII. Mean tissue concentrations of F-113
in rats exposed to 0.2% F-113
for 7 and 14 days (Carter, 1970)

TISSUE	EXPOSURE		POSTEXPOSURE	
	7 Day	14 Day	24 Hours	48 Hours
Brain ug/gm	22.73 (1.00)	22.65 (1.33)	None	None
Liver ug/gm	15.77 (0.87)	16.40 (1.72)	None	None
Heart ug/gm	16.59 (2.56	15.03 (2.51)	None	None
Fat ug/gm	722.48 (71.29)	659.24 (21.17)	108.45 (33.62)	5.60 (2.94)
Adrenal ug	8.39 (2.61)	3.47 (0.34)	None	None
Thyroid ug	1.09 (0.46)	0.94 (2.00)	None	None

( ) Standard Deviation

The major difference in these findings from those presented for F-11 and F-12 is that for F-113 almost all of the concentration occurs in the fat while adrenal levels are relatively low and even decrease as exposure continues. It must be emphasized that the exposures to F-11 and F-12 were only for five minutes. The possibility of rapid uptake by the adrenals during initial exposure followed by active elimination of fluorocarbons from the adrenals during exposure may be worth exploring. That the various other organ levels did not alter significantly from the seven to the fourteen-day exposures is consistant with the idea that such concentrations will stabilize as equilibria between ambient air concentration, blood level, and tissue levels are reached. However, there is some indication that levels of F-11 and F-12 in various tissues may alter during prolonged exposure as less accessible tissues are reached (Blake and Mergner, 1974).

Similar tissue distribution studies have also been done on rats with short term exposure to H-2402 (Griffen *et al.*, 1972). The results are given in Table XLIII.

Table XLIII. Tissue concentrations of H-2404 in rats after 30 minutes exposure to 3.7% H-2402 (Griffin *et al.*, 1972)

	Post-Inhalation Interval (Hrs)			
Tissue	0	1-1/2	3	24
Liver	258[a]	5	2	0.28
Lung	44	18	2	0.18
Brain	0.70	2.1	0.78	0.36
Kidney	82	27	23	0.33
Heart	24	2.1	2	1.1
Muscle	73	19	2.8	1.0
Fat	365	469	410	11
Blood	87	7	0.23	0.22

[a] All values shown are in μg -2402/g tissue.

Increase of H-2402 levels in the fat and brain tissue from immediately after inhalation to one and a half hours after inhalation indicates that the 30 minute exposure period was not long enough for equilibrium to be reached. Like F-11, F-12 and F-113, large amounts of H-2402 are stored in fat tissue. The most striking value, however, is the large amount found in the liver immediately after inhalation and its rapid elimination after one and a half hours. Similar levels of liver uptake have not been noted for other fluorocarbons under discussion. The anesthetic, halothane ($CHBrCl-CF_3$), however, is transported to the liver where it is apparently metabolized to trifluoroacetic acid (Rosenburg, 1972; Cascorbi and Blake, 1971; Cohen, 1969). A similar pattern for H-2402 has not been proposed and would not seem indicated - although it cannot be ruled out - on the basis of what is known of its toxic effects.

Van Stee and Back (1971a) have monitored the levels of H-1301 in blood, brain, and heart tissue during five-minute exposures to 71-76% H-1301. The results are given in Figure 21.

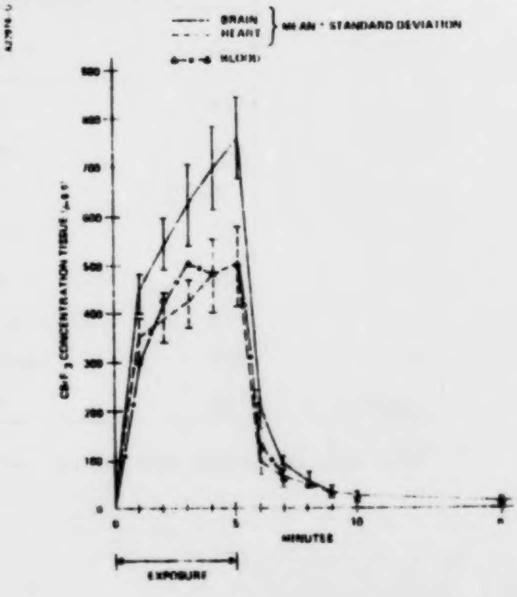


Figure 21. Rat brain and heart concentrations of $CBrF_3$ during and after 5-minute exposures to 71-76% $CBrF_3$ in O_2 (n=10, mean ± SD). The ▲-•-▲ line represents blood concentrations of $CBrF_3$ observed during an experiment in which the conditions were similar to those of the brain-heart experiments (n=1) (Van Stee and Back, 1971a).

As Figure 21 indicates, H-1301 concentration in the brain increased twice as rapidly and reached levels 50% above those of the heart and blood. Further, levels of H-1301 two minutes following exposure were significantly higher in the brain than the heart. This pattern probably reflects the lipid solubility of H-1301 which is more concentrated in the central nervous system than the heart because of the high lipid concentration of the former as compared to the latter (Van Stee and Back, 1971a).

Sherman (1974) has studied tissue distribution of F-12 in rats and dogs over one and two years of oral administration. A summary of the results is given in Tables XLIV and XLV.

Table XLIV. Tissue distribution* of residual F-12 in control rats and in rats fed 0.2% (w/v) and 2.0% (w/v) F-12 over a two year period (Sherman, 1974)

	Year	MALE				FEMALE			
		mg administered				mg administered			
		0	0	Low	High	0	0	Low	High
Adrenals	1	< 0.06	< 0.04	< 0.04	< 0.06	< 0.07	< 0.06	< 0.04	< 0.04
	2	1.22	0.35	2.11	1.34	0.68	0.67	1.38	1.64
Blood	1	< 0.01	< 0.01	< 0.01	< 0.04	< 0.01	< 0.01	< 0.01	< 0.01
	2	< 0.04	< 0.04	< 0.05	< 0.05	< 0.04	< 0.04	< 0.05	< 0.05
Bone Marrow	1	0.05	< 0.03	< 0.03	< 0.03	0.11	< 0.06	< 0.04	0.07
	2	< 0.01	0.49	0.74	0.56	< 0.01	1.70	0.71	1.70
Brain	1	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	2	< 0.06	< 0.06	< 0.10	< 0.12	< 0.06	< 0.10	< 0.10	< 0.12
Fat	1	< 0.01	< 0.01	0.13	2.28	< 0.01	< 0.01	0.11	1.15
	2	< 0.02	< 0.01	0.17	0.86	< 0.02	< 0.01	0.04	0.71
Heart	1	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02
	2	< 0.02	< 0.02	< 0.02	< 0.02	< 0.01	< 0.01	< 0.02	< 0.01
Kidney	1	< 0.02	< 0.02	< 0.02	< 0.02	< 0.03	< 0.03	< 0.03	< 0.03
	2	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Liver	1	< 0.01	< 0.01	< 0.01	0.05	< 0.01	< 0.01	< 0.01	< 0.01
	2	< 0.01	< 0.01	< 0.01	0.02	< 0.01	< 0.01	< 0.01	< 0.01
Muscle	1	< 0.03	< 0.03	< 0.03	< 0.03	< 0.03	< 0.03	< 0.03	< 0.03
	2	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

* ppm = μg/ml blood or μg/g wet tissue.

Table XLV. Tissue distribution* of residual F-12 in control dogs and dogs fed 0.03% and 0.3% F-12 over a two year period (Sherman, 1974)

	Year	MALE			FEMALE		
		ppm administered			ppm administered		
		0	300	3,000	0	300	3,000
Adrenals	1	< 0.01	-	< 0.01	< 0.01	-	< 0.01
	2	1.04	1.23	0.88	1.73		1.50
Blood	1	< 0.01	-	< 0.01	< 0.01	-	< 0.01
	2	< 0.04	< 0.04	< 0.04	< 0.02	< 0.02	< 0.02
Bone Marrow	1	< 0.08	-	< 0.07	< 0.05	-	-
	2	0.47	0.45	0.65	0.50	1.16	1.55
Brain	1	< 0.01	-	< 0.01	< 0.01	-	< 0.01
	2	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09
Fat	1	< 0.01	-	0.25	< 0.01	-	0.52
	2	0.02	0.23	0.12	0.15	0.34	1.19
Heart	1	< 0.02	-	< 0.02	< 0.02	-	< 0.02
	2	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Kidney	1	< 0.01	-	0.01	< 0.01	-	< 0.01
	2	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Liver	1	< 0.01	-	< 0.01	< 0.01	-	< 0.01
	2	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Muscle	1	< 0.03	-	< 0.03	< 0.03	-	< 0.03
	2	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

* ppm = μg/ml blood or μg/g wet tissue.

In rats, there seems to be some indication of tissue storage by the adrenals, bone marrow, and fat. However, the relatively high concentrations of a compound with the same peak retention time found in control animals may indicate either interference from an unrelated material or contamination of the controls with F-12. A similar pattern is seen in the results of dog feeding studies. Because the postulated interferring agent was not identified, the quantitative significance of these findings is difficult to assess (Sherman, 1974).

From the information presented on absorption, elimination, transport, and distribution, the following general scheme of fluorocarbon uptake seems evident. Fluorocarbons are absorbed and transported by the blood. Absorption takes place primarily across the alveolar membranes. The amount and rate of absorption depends upon a variety of factors including the physical and chemical characteristics of the particular fluorocarbon, the concentrations of the fluorocarbon in the ambient air, breathing patterns, and possibly individual differences in ability to absorb these compounds. If exposure is sufficiently long, an equilibria is reached among ambient air, blood, and tissue concentrations. The fluorocarbons, being more lipid than water soluble, seem to concentrate in areas of high lipid content. All of the studies monitoring fat tissue indicate some degree of concentration in fat. The high adrenal levels of F-11 and F-12 (Allen and Hansbury Ltd., 1971) and brain levels for H-1301 (Van Stee and Back, 1971a) do not represent equilibrium values. Carter (1970), however, in seven and fourteen-day exposures did note higher concentrations of F-113 in the brain than in the heart comparable to those for H-1301. Similarly, Sherman (1974) in long term feeding studies did note some degree of adrenal concentration for F-12 but its relevance to extremely high values noted by Allen and Hansbury, Ltd. for F-11 and F-12 (1971) is limited. Thus, until more information becomes available on equilibria concentration of a wider variety of fluorocarbons, the most that can be suggested concerning tissue distribution is that, depending upon the lipid solubility of the fluorocarbon, tissues with a higher lipid content than blood will probably concentrate fluorocarbons from the blood. The relative amounts of fluorocarbons absorbed by body tissue will probably correspond to the relative order of absorption by blood from the air as outlined in the section on absorption/elimination.

C. Metabolic Effects

The fluorinated propellants, solvents, and fire extinguishing agents are notable for their relatively low liver toxicity when compared to other halocarbons such as carbon tetrachloride and halothane (see Section XII, Toxicity to Birds and Mammals). Both halothane and carbon tetrachloride inhibit oxidative-phosphorylation in rat liver mitochondria (Snograss and Pinas, 1965). The fluorocarbons under consideration in this review do not, for the most part, seem to behave in this manner.

As indicated in Figures 22 & 23, Griffin and coworkers (1972) have shown that a variety of fluorocarbons do not markedly effect oxygen consumption or oxidative phosphorylation in isolated mitochondria from rats exposed to fluorocarbons prior to mitochondrial isolation.

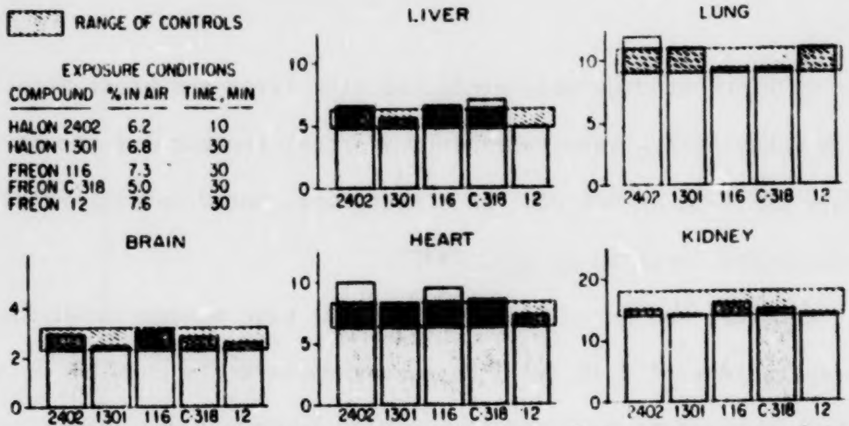
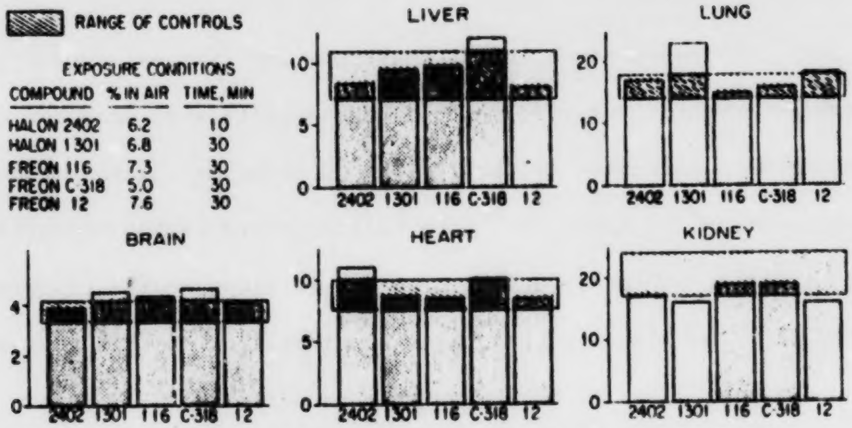


FIGURE 22. Oxygen consumption in mitochondria from rats exposed to halocarbons. Mitochondria were isolated from tissues after the rats were exposed under the indicated conditions. Mitochondria from controls were assayed simultaneously with the experimental groups and the range of activities includes data from all five groups of controls. The rate of oxygen consumption is expressed as mμ AO consumed/mg protein /min X 10^{-1}. (Griffin et al., 1972)



EXPOSURE CONDITIONS

COMPOUND	% IN AIR	TIME, MIN
HALON 2402	6.2	10
HALON 1301	6.8	30
FREON 116	7.3	30
FREON C 318	5.0	30
FREON 12	7.6	30

FIGURE 23. Oxidative phosphorylation in mitochondria from rats exposed to halocarbon. Mitochondria were isolated from tissues after the rats were exposed under the indicated conditions. Mitochondria from controls were assayed simultaneously with the experimental groups and the range of activities included data from all five groups of controls. The rate of phosphorylation is expressed as mμ Moles P_i esterified/mg protein/min X 10^{-1}. (Griffin *et al.*, 1972)

Further *in vitro* studies were conducted with liver and heart mitochondria in which measurements were taken during actual exposure of the mitochondria to either 20% F-12 or H-1301. No effects were noted on either oxidation or phosphorylation (Griffin *et al.*, 1972).

However, Van Auken and Wilson (1973) have demonstrated that F-21 at concentrations of 0.1% (w/v) decreases respiratory control and ADP/O ratio in mitochondria isolated from rabbit liver and mung bean.

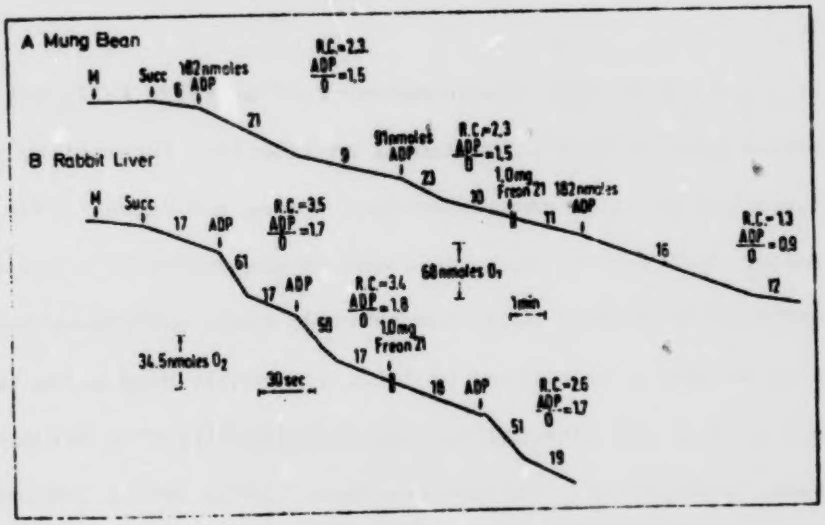


Figure 24. The effect of Freon-21 on coupling parameters of rabbit liver and mung bean mitochondria. A) Mung bean. The reaction mixture of 3.2 ml contained: 0.3 M mannitol, 4 mM $MgCl_2$, 2 mM $K\text{-}PO_4$, pH 7.4, 50 mM tris-ticine, pH 7.4. Additions include: M Mitochondria (0.15 mg protein), 8 mM Na-succinate pH 7.4, R.C. respiratory control. Numbers on traces are μmoles O_2per min. B) Rabbit liver. The reaction mixture of 1.5 ml contained: 0.2 M mammitol, 10 mM tris-tricine, pH 7.2, 4 mM $MgCl_2$, 2 mM $K\text{-}PO_4$, pH 7.2, 8 mM succinate and approximately 0.7 mg protein. ADP was added as 85 nmoles per aliquot. (Van Auken and Wilson, 1973); reprinted with permission from Springer-Verlag, Copyright 1973.

The above data would seem to suggest at least some loss of respiratory control. However, the respiration rates are not altered by F-21 indicating that it is not a typical uncoupling agent (Van Auken and Wilson, 1973).

A number of investigators have been concerned with the possible binding of fluorocarbon molecules to portions of biologically important macromolecules. Nunn (1972) has postulated a general theory of anesthesia involving a Van der Waal's attraction between the anesthetic and hydrophobic areas of macromolecules including proteins. Halsey (1974) speculates, on the basis of N.M.R. data, that fluorocarbons such as F-12, F-22, F-14, and F-116 may behave similarly to conventional anesthetics, interacting with various hydrophobic sites in macromolecules. Young and Parker (1972), however, propose that F-12 at least is bound to the hydrophilic areas of various phospholipids in that potassium chloride stops arrhythmia induced by epinephrine in hearts sensitized by F-12, apparently displacing the F-12 molecule held by the phospholipid (see Section XII, D-1, Epinephrine Induced Cardiac Arrhythmia). Cox and coworkers (1972a and b) indicate the F-11 binds to the phospholipids in the liver cytochrome P-450. Epstein and coworkers (1967b) indicate that unspecified fluorocarbons induce liver microsomal enzyme synthesis. Thus, while the lipid soluble fluorocarbons may complex with a variety of macromolecules and possibly effect lipid membrane systems, no clear correlation can yet be drawn between this possibility and their biological activity.

D. Metabolism

Just as the fluorinated propellants, solvents, and fire extinguishing agents seem to differ significantly from other low molecular weight halocarbons in metabolic effects, so do they differ in metabolism. The toxic effects of both carbon tetrachloride and halothane have been linked to their enzymatic dehalogenation involving free radical formation (Slater and Sawyer, 1971; Rosenburg, 1972). Although such biotransformation cannot be ruled out over periods of prolonged exposure at low concentration and low rates of transformation, there is little hard evidence as yet to indicate that significant metabolism does occur.

Of the fluorocarbons under review, only the fluoromethanes F-11 and F-12 are topics of published reports on metabolism. Cox and coworkers (1972a) have attempted to demonstrate possible reductive dehalogenation of F-11 in two ways. First, reasoning that the primary products of dehalogenation would be F-21 and F-112, they incubated F-11 in microsomal preparations from rats and chickens and from rats, mice, guinea pigs and hamsters pretreated with phenobarbital to stimulate metabolism. No F-21 was detected. Secondly, as an index of free radical formation, they measured the effect of F-11 on lipid peroxidation. No evidence of free radical formation was found (Cox *et al.*, 1972a).

Blake and Mergner (1974) have studied the possible metabolism in beagles of both F-11 and F-12 using carbon-14 labelled compounds. The radiolabelled impurities in F-11 (89.6% pure) were 9% $^{14}CCl_4$ and 1.4% $^{14}CHCl_3$. The radiolabelled impurities in F-12 (96.0% pure) were $^{14}CF_3Cl$ and/or $^{14}CF_4$.

Exposures to F-11 ranged from concentrations of 0.19% to 0.55% for periods of from six minutes to twenty minutes. Exposures to F-12 ranged from concentrations of 0.82% to 11.8% over the same periods. The results are summarized in Tables XLVI and XLVII.

Table XLVI. Recovery and Inhalation of F-11 and F-12 in Beagles (adapted from Blake and Mergner, 1974).

	Recovery of Radioactivity (Percent of Inhaled Dose)			
	Exhaled Unchanged	Exhaled as CO_2	Urine	Total
F-11	101.6 ± 14.3	0.30 ± .13	0.0095 ± .007	101.8 ± 13.8
F-12	103.0 ± 6.2	0.14 ± .04	0.04 ± .02	103.2 ± 6.3

Table XLVII. Tissue Concentrations of Non-volatile Radioactivity in Beagles 24 hours after Inhalation of F-11 and F-12.

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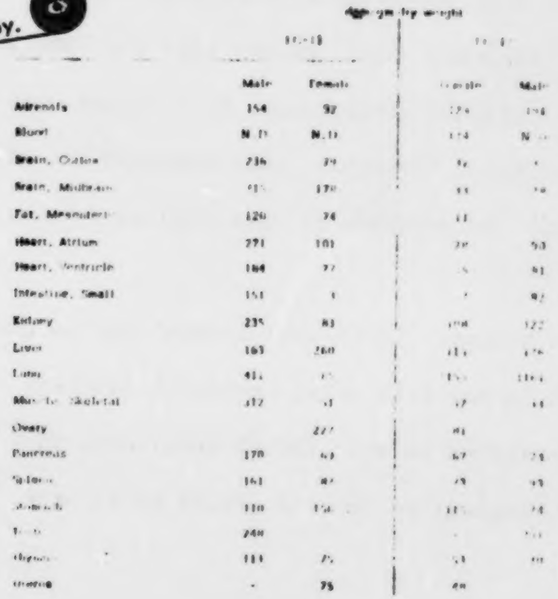

	dpm/gm dry weight			
	F-11		F-12	
	Male	Female	Female	Male
Adrenals	154	97	[illegible]	[illegible]
Blood	N.D.	N.D.	[illegible]	N.D.
Brain, Cortex	236	[illegible]	[illegible]	[illegible]
Brain, Midbrain	[illegible]	170	[illegible]	[illegible]
Fat, Mesenteric	120	74	[illegible]	
Heart, Atrium	271	101	[illegible]	53
Heart, Ventricle	164	[illegible]	[illegible]	61
Intestine, Small	151	[illegible]	[illegible]	[illegible]
Kidney	235	83	[illegible]	[illegible]
Liver	163	260	[illegible]	[illegible]
Lung	[illegible]	[illegible]	[illegible]	[illegible]
Muscle, Skeletal	[illegible]	[illegible]	[illegible]	[illegible]
Ovary		[illegible]	[illegible]	
Pancreas	170	[illegible]	67	[illegible]
Spleen	161	[illegible]	[illegible]	[illegible]
Stomach	110	[illegible]	[illegible]	[illegible]
Testis	248		[illegible]	[illegible]
Thyroid	111	[illegible]	[illegible]	[illegible]
Uterus	-	75	[illegible]	

For both F-11 and F-12, the total recovery of $^{14}CO_2$ and non-volatile urinary and tissue reactivity equals about 1% of the administered dose. Because the radioactive impurities in the F-11 sample, carbon tetrachloride (9%) and trichloromethane (1.4%) are both known to be metabolized in animals, the F-11 studies gives no firm evidence for fluorocarbon metabolism. However, in the F-12 study, all of the administered radioactivity was in the form of fluorocarbons: 96% F-12 and 4% F-13 and/or F-14. According to the current view of fluorocarbon biological activity, increasing fluorination leads to increasing stability (Clayton, 1970). Consequently, if any or all of these compounds were to be metabolized, F-12 would probably be the most readily metabolized. F-12 study thus seems to give a rather sound indication that about 1% of F-12 - and/or F-13 and F-14 - are metabolized after relatively brief exposures.

Eddy and Griffith (1971) have obtained results on the metabolism of carbon-14 labelled F-12 in rats on oral administration showing a somewhat greater degree of metabolism. About 2% of the total dose is exhaled as CO_2 and about 0.5% excreted in the urine. By thirty hours after administration, the fluorocarbon and its metabolites are no longer present in the body.

Further studies on the metabolism of fluorocarbon propellants, solvents, or fire extinguishing agents have not been encountered. The current view of metabolism of the fluorinated anesthetic halothane, however, is given in Figure 25.

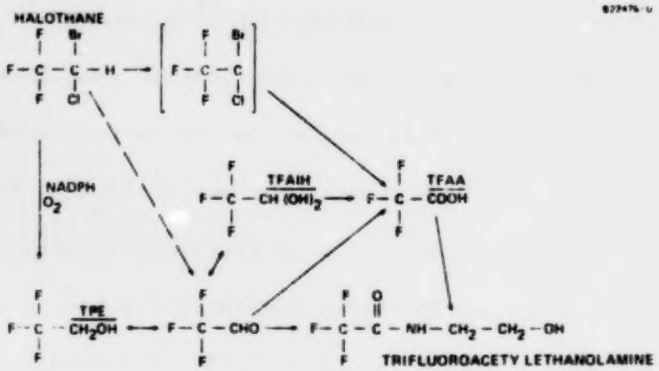

Figure 25. Possible Metabolic Pathways for Halothane
(from Rosenburg, 1972)

A number of other fluorocarbons seem to follow a similar pattern. Fluoroxene (trifluoroethyl vinyl ether) may be metabolized to trifluoroethanol in mice or trifluoroacetic acid in man (Cascorbi and Singh-Amaranath, 1972). Hexafluorodichlorobutene may also be metabolized to trifluoroacetic acid and other unidentified acids (Truhant et al., 1972). In the metabolism of halothane, it should be noted that all biotransformations take place in the non-fluoro-substituted carbon. In the commercially important fluoroethanes, this type of metabolism would not be expected in that both carbons usually are fluorosubstituted making both more refractory to biotransformation. However, the study of F-12 metabolism by Blake and Mergner (1974) would seem to indicate that fluorosubstitution of both carbons would not in itself preclude metabolism. As these investigators indicate, the apparent resistance of these compounds to metabolic degradation may be more a function of their rapid elimination rather than chemical or biological stability. Over longer periods of exposure, the fluorocarbons will not only be in equilibria with tissue for longer periods but also will be more likely to reach less accessable "deep" tissue compartments. Metabolic tests requiring longer exposure periods will be necessary to assess the significance of such multicompartment distribution (Blake and Mergner, 1974). However, it would not be surprising if further studies show that a variety of fluorocarbons undergo biotransformation. In fact, at low level exposures that would be found in the general environment or home, such metabolism might be facilitated by the lack of substrate or product inhibition (Halsey, 1974).

The significance of fluorocarbon metabolism is difficult to assess with certainty because so little is actually known. Often, of course, a compound may be metabolized to a compound of greater toxicity, such as halothane to trifluoroacetic acid. Truhaut and coworkers (1972) have noted a pattern in 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene-2 [DCHFB] of delayed death similar to that noted in 1-chloro-1,2,2-trifluoroethylene (Walther _et al_., 1970).

Table XLVIII. Delayed Death After DCHFB Administration to Rabbits [Truhaut _et al_., 1972]

Concentration Exposure time	500 ppm 1 hour	200 1 hour	100 1 hour	200 30 min.	200 15 min.
Delayed Death	85 min. to 3 1/2 hours	12 hours	4 days	3 days	0

Such a delay may indicate that a metabolite rather than the parent compound may be the toxic agent (Truhaut _et al_., 1972). Patterns of delayed death have also been noted for various fluorocarbons under review and will be considered in the appropriate sections. However, without clearer experimental evidence on the possible metabolism of these fluorocarbons, delayed death cannot be viewed as indicative of toxic metabolites.

X. ENVIRONMENTAL TRANSPORT AND FATE

A. Persistence

The chemical stability of the commercial fluorocarbons would lead one to believe that the compounds are very persistent in the environment. The ability to monitor at least fluorocarbon 11 in relatively isolated parts of the Atlantic Ocean (Lovelock et al., 1973) tends to support this contention. However, the degree of persistence is relatively unknown. Lovelock et al. (1973) have suggested a residence time of 10 years. This assumes no significant surface or tropospheric degradation and complete destruction in the stratosphere (Lovelock, 1974). The transfer time to the stratosphere sets the lower limit of 10 years. Su and Goldberg (1973) have suggested a residence time of 30 years for fluorocarbon 12. The basis of this assignment is unknown.

B. Biological Degradation

Information on the biodegradability of the commercial fluorocarbons is not available. However, their volatility would certainly limit, if not preclude, biodegradation. Goldman (1972) has reviewed the enzymology of carbon-halogen bonds and suggested that although fluorines substituted in the 2-position of short-chain fatty acids (e.g., fluoroacetate) are replaced by hydroxyl groups, the high strength of the carbon-fluorine bond would indicate a high biological stability in other compounds. And, in fact, with any other compound containing the carbon-fluorine bond, with the exception of fluoroacetate (e.g., trifluoroacetate, difluoroacetate, 2-fluoroproprionate, and 3-fluoroproprionate), fluoride release could not be detected.

C. Chemical Stability in the Environment

Three studies have examined the stability of fluorocarbons under atmospheric conditions. Japar et al. (1974), Hester et al. (1973), and Saltzman et al. (1966) have all photolyzed fluorocarbons under varying conditions and found no decomposition. Both Hester et al. (1973) and Japar et al. (1974) used simulated smog conditions. Hester et al. (1973) photolyzed fluorocarbons 11 and 12 in an ambient air sample for two months and found no reaction. Saltzman et al. (1966) exposed a gaseous mixture of $CBrF_3$ and C_4F_8 to ultraviolet light, water vapor, ozone, SO_2, and diluted automobile exhaust and reported no degradation.

D. Environmental Transport

Because of the high vapor pressures of the fluorocarbon compounds, the major environmental transportation route is through the atmosphere. For example, Lovelock (1972) has determined that trichlorofluoromethane concentrations of rural southern England and Ireland can be attributed to sources on the European continent.

E. Bioaccumulation

Because of the high volatility of the compounds under consideration, the possibility of bioaccumulation seems rather remote. Information on this possibility is not available.

XI. HUMAN TOXICITY

A. Accidental Exposures and Misuse

Fluorocarbon propellants - primarily F-11 and F-12 - have been associated with the broader problem of abusive inhalation of aerosols. In an attempt to achieve an intoxicated state, the aerosol is sprayed into a bag, the bag placed over the mouth and nose, and the contents inhaled deeply. In other cases, the bag containing concentrated aerosols is placed over the head (Crooke, 1972). This procedure presents two potential hazards, the aerosol itself and asphyxiation. Many of the early reports of aerosol abuse, while recognizing the intoxicating effects of the fluorocarbons, assumed on the basis of the then current understanding of fluorocarbon toxicity that suffocation was the probable cause of death in fatal exposures (Coleman, 1968; Hoffmann, 1968). However, as this practice became more wide spread, cases in which asphyxiation could not be the cause of death became apparent. Bass (1970) describes one hundred and ten such deaths occurring between 1962 and 1969, fifty-seven of which were associated with fluorocarbon propellants. These deaths sometimes involved rigorous activity during or immediately after inhalation, followed by the rapid onset of death thus ruling out suffocation as the cause of these deaths. Bass (1970) concluded that these deaths were probably caused by cardiac arrhythmia, possibly aggravated by elevated levels of catecholamines due to stress and/or moderate hypercapnia. This deduction was subsequently supported by a variety of investigators who found that many fluorocarbons can sensitize the hearts of various mammals to epinephrine induced arrhythmias and that this effect may be magnified by an increase in blood carbon dioxide (e.g., Reinhardt et al., 1971).

A similar concern over the role of fluorocarbons in causing human deaths has been expressed in cases of possible over use by asthmatics of bronchiodilator drugs in aerosol nebulizers propelled by various fluorocarbons (Taylor and Harris, 1970a). Such nebulizers deliver a fixed amount of fluorocarbon gases and bronchiodilator drugs per actuation. Two of the more commonly cited formulations Medihaler-Iso® and Isuprel Mistometer® release 12.5 ml propellant (F-12 and F-114) and 5.8 ml propellant (F-11, F-12, and F-114) per actuation, respectively. In an acute asthmatic attack, Taylor and Harris (1970a) postulate that these propellants may be inhaled in sufficient quantities to cause cardiac arrhythmias. As with instances of abusive inhalation, stress and oxygen deficiency may be contributing factors. Although supported by some epidemiologic evidence (see Part D of this section), there is little hard data to indicate that this does occur in man. However, this possibility has stimulated intense investigation and considerable controversy in studies of laboratory animals (see Part D, Section XII, Cardiac Effects of Fluorocarbons).

Clayton (1966) reports that approximately one liter of cold F-113 was accidently released into the stomach of an anesthetized patient. The immediate effect of this exposure was transient cyanosis. For the next three days, the patient experienced severe rectal irritation and diarrhea.

B. Occupational Exposure and Normal Use

The fluorocarbon gases have not presented a documented hazard in terms of industrial hygiene and occupational safety. In 1952, Mendelhoff associated chronic exposure to F-12 with malaise, chills, fever, nausea, abdominal pain and eventual death in a repair mechanic for refrigeration equipment. However, in that exposure to methyl chloride and sulfur dioxide as well as a moderate degree of alcoholism for several years were also noted, this isolated case cannot be construed as a substantial indication of F-12 toxicity. A similar case reported by Marti (1948) also included exposure to sulfur dioxide and F-12 thermal decomposition products and thus cannot be considered as indicative of F-12 human toxicity. In a recent study, women using an average of 21.6 g of fluorocarbon propellants per woman per day for four weeks did not evidence any adverse effects of measurable fluorocarbon blood levels. The investigators estimate that the average exposure of the test subjects was over nine times the amount normally used (Marier et al, 1973).

A group of fifty workers who were exposed to F-113 for a period of up to four and a half years (mean 2.77 years) were evaluated for possible adverse effects from concentrations of 46 to 4,700 ppm (mean 669 ppm; median 435 ppm). No signs of toxicity were noted (Imbus and Adkins, 1972).

Only one investigator has implicated the fluorocarbons with a serious health problem. Good (1974) contends that fluorocarbons used as aerosol propellants may be a major cause of lung cancer in the United States. This hypothesis is based largely on clinical data without follow-up animal experiments. Sputum cytological techniques are used in which changes are classified in five stages--Class I being normal and Class V showing marked atypia. In a group of 200 heavy aerosol users, precancerous changes of lung cells were noted in each individual which were reversed when aerosol use was discontinued. In a second study (Good et al., 1974) comparing 50 heavy users to 250 non-users or light users, 12 of the heavy users showed moderate to marked atypical cell changes which were seen in only two of the non-user/light user group. Good (1973) found that use of even such innocuous agents as breath fresheners in aerosols will result in Class III changes in 4-5 months. The resulting clinical syndrome, polymyalgia rhumatica, is described as a low-grade fever, emotional upsets, without coughing. The etiological progression is presumed to be ciliary paralysis resulting in chronic gram negative infection of the lung. These organisms may produce a mild toxin which causes the clinical symptoms and atypical changes in the lung. A number of investigators are currently conducting research in this area (Archer, 1974).

C. Controlled Human Studies

Exposure to humans under experimental conditions has been thus far restricted to three of the most common fluorocarbons: F-12, F-113, and F-1301. Of these, F-1301 has received by far the most attention because of its use as a fire extinguishing agent.

Fluorocarbon-12 has been tested using human subjects by both Kehoe (1943) and Azar and coworkers (1971). Kehoe (1943) exposed one subject to concentrations of 4%, 6%, 7%, and 11% for periods of 80, 80, 35, and 11 minutes, respectively. A second subject was exposed to 4% for 14 minutes immediately followed by 2% for 66 minutes. At 4% F-12, the subjects experienced a tingling sensation, humming in the ears, and apprehension. Electroencephalographic changes were noted as well as slurred speech and decreased performance in psychological tests. In the one subject exposed to higher concentrations, these signs and symptoms became more pronounced with increases in concentration. An exposure of 11% caused a significant degree of cardiac arrhythmia followed by a decrease in consciousness with amnesia after ten minutes. At concentrations of 1% F-12 for 150 minutes, Azar and coworkers (1972) noted only a 7% decrease in psychomotor test scores and no effects at 0.1% concentration over the same period.

Fluorocarbon-113 has been tested on human subjects by Stopps and McLaughlin (1967) and Reinhardt and coworkers (1971). Psychomotor performance was evaluated with exposures to 0.15%, 0.25%, 0.35%, and 0.45% F-113 for 165 minutes (Stopps and McLaughlin, 1967). At the lowest level, no effect was noted. At 0.25% there was difficulty in concentrating and some decrease in test scores. These effects were more pronounced at 0.35% F-113. At 0.45% F-113, performance at various tasks was decreased by between 10% and 30%. These decreases coincided with sensations of "heaviness" in the head, drowsiness, and a slight loss of orientation after shaking the head from left to right. Reinhardt and coworkers (1971) exposed human subjects to concentrations of 0.1% and 0.05% F-113 for 180-minute periods in the morning and afternoon on five days. No decreases in psychomotor ability were noted. No abnormal findings were noted during post-exposure physical examination, hematologic and blood chemistry tests (conducted three days after final exposure) and steady-state measurements of diffusing capacity of lungs and fractional uptake of carbon monoxide.

Fluorocarbon-1301 exposures to human test subjects have been summarized by Reinhardt and Reinke (1972). Concentrations of 1%, 3%, and 5% F-1301 for periods of three to three and a half minutes had no effect on electrocardiograms or response times in three subjects. Concentrations of 7% and 10% over the same period, however, did result in slight lessening of equilibrium and increase in response time (Reinhardt and Stopps, 1966). Similar results were obtained at Hine Laboratories (1968) over longer durations. Concentrations of 5% for 20-25 minutes caused a minimal decrease in psychomotor performance while concentrations of 10% caused a more pronounced decrease in ten subjects. Drowsiness and an increased sense of well-being were also noted. Graded concentrations of 5-17% H-1301 over periods of 15-20 minutes resulted in central nervous system effects ranging from tingling to a feeling of impending unconsciousness (14% H-1301) in nine out of ten subjects, with the remaining subject reporting no effects at concentrations up to 15.7%. Cardiac effects were noted in only three of the ten subjects. Effects in two subjects at 8.2-15.7% H-1301 were primarily T-wave alterations (depression and flattening), with increased sinus arrhythmias occurring in one of these subjects. The third subject showing cardiac effects exhibited T-wave flattening after an initial exposure to 16.9% H-1301 but 36 hours later, after a five-minute exposure to 14% H-1301, developed cardiac arrhythmias including T-wave flattening, extrasystoles forming bigeming, A-V dissociation, and multifocal premature beats. Clark (1970) has also noted T-wave depression and tachycardia along with loss of equilibrium and paresthesia in all subjects after less than a one-minute exposure to 12% and 15% H-1301. T-wave depression was noted at 10% exposures for one minute in two subjects, along with slight dizziness and paresthesia. Three-minute exposures to 9% and 6% resulted in similar central nervous system effects and tachycardia but no arrhythmias. In addition to these studies, Call (1973) exposed eight subjects to concentrations of 4% and 7% H-1301 for three minutes in a hypobaric chamber maintained at 760 mm Hg, 632 mm Hg (equivalent to 5,000 feet), and 380 mm Hg (18,000 feet). Although no cardiac effects were noted in any exposures, reaction times were increased from about 550 milliseconds to about 600 milliseconds at both concentrations and at all altitudes.

Halon-1211, another fire extinguishing agent, has been administered to humans at concentrations of 4-5%. After 30-40 seconds, the subjects became dizzy and light-headed. These symptoms increased after one minute and were accompanied by paresthesia of the fingers and toes. One subject, exposed for two minutes, showed central nervous system stimulation and a transient cardiac irregularity. Recovery was rapid and without noticeable after-effects (Clark, 1972).

D. Epidemiology

In the narrowest sense, epidemiological investigations have not been conducted and would not seem to apply to these fluorocarbons. As indicated in a previous section, these compounds have not presented an appreciable hazard in manufacture and although they are commonly used in most households, no wide-spread adverse effects have been unequivocably attributed to these compounds under normal use. The patterns of abusive inhalation have been studied by Bass (1970) and reviewed by Crooke (1972). The abuse first appeared on the west coast in the early 1960's, moved eastward and apparently gained some popularity by 1967, and has persisted at least into 1972. Fluorocarbons, while the most popular, are only one of many classes of compounds used in this practice; others include toluene, benzene, trichloroethylene, acetone, and isopropyl alcohol. Kilien and Harris (1972) have reported that over 140 cases of death from abusive inhalation of aerosol propellants have been documented. These deaths have occurred in individuals from 11 to 23 years of age, with the majority coming from middle-income families (Bass, 1970). Such studies are of little use in assessing the environmental hazard of fluorocarbons since they indicate only the potential for fatal abuse under environmentally unrealistic conditions.

Taylor and Harris (1970b) have associated increasing deaths in England due to asthma with increasing use of fluorocarbon propelled bronchodilators. The potential role of fluorocarbon propellants in such deaths has also been underscored by Archer (1973). In England, asthmatics have been found dead with empty aerosol nebulizers in their hands and in other cases patients have been known to use two nebulizers prior to death (Taylor and Harris, 1970b). However, such evidence is, at best, highly circumstantial. While not denying the potential danger from overuse of these nebulizers, a variety of factors must be considered in asthma deaths before a correlation can be accepted as a cause-effect relationship (Silverglade, 1971b).

XII. TOXICITY TO BIRDS AND MAMMALS

A. Acute Toxicity

1. Acute Inhalation Toxicity

A variety of fluoromethanes and ethanes, including those of commercial importance, have been tested for acute inhalation toxicity in standard laboratory mammals. For the most part, these tests have attempted to evaluate either the human health hazard from occupational exposure (e.g., Desoille _et_ _al_., 1973; Steinberg _et_ _al_., 1969; Yant _et_ _al_., 1932) or their anesthetic potency (e.g., Carpenter, 1954; Miller _et_ _al_., 1967; Van Poznak and Artusio, 1960). Thus, much of the information is given in terms of lethality, loss of responsiveness, or other adverse effects such as convulsions or tremors. Summaries of the available data are given in Tables IL-LIV. In these tables, some attempt is made to give dose-response relationships by using five response categories. Approximate lethal concentration (ALC) is the minimum concentration causing death in any of the animals over a given exposure period and is usually only somewhat less than the concentration causing death in half of the exposed animals (LC_{50}). The anesthetic concentrations usually represent the concentration at which certain basic reflexes are lost; e.g., the righting reflex. The concentration causing tremors is used rather than the concentrations causing convulsions because the former usually represents the minimum concentration causing any marked response. It will be noted that the concentration causing tremors is usually below that causing anesthesia; thus most of the fluorocarbons are not satisfactory anesthetics. The non-lethal concentration is admittedly somewhat ambiguous. In most cases, it merely represents a concentration not causing death. However, in instances where it is lower than the tremor concentration, the non-lethal concentration is a reasonable approximation of the "no marked effect" level. In a few cases, important observations not fitting the above categories are included in brackets. Information not supplied in the original study is indicated by "N.S.".

Many review articles, especially those of Clayton (1962, 1966, 1967a and b, 1970) have emphasized the relationship between fluorination and toxicity: as the degree of fluorination increases in a given series, the toxicity decreases. This relationship and the relationships between the various groups presented in Tables IL-LIV are given in Figure 26 using LC_{50}'s or ALC's. To make the comparison as valid as possible, preference is given to data on rats and exposure periods of four hours. Values of less than one-half hour or greater than six hours are not used. In cases where there is more than one compound in a single category, the most halogenated is plotted first.

Table IL. Acute Inhalation Toxicity of Perhalomethanes in Laboratory Mammals.

Fluorocarbon	Code	Animal	Responses					Duration	Reference
			ALC	LC_{50}	Anesth.	Tremors	Non-lethal		
CCl_3F	F-11	Rats	6%					4 hr.	Waritz, 1971
			10%					20-30 min.	Lester and Greenburg, 1930
			20%					5 min.	Kuebler, 1964
				15%				30 min.	Paulet, 1969
					10%			20 min.	Keubler, 1964
					<9%			N.S.	Lester and Greenburg, 1950
						3.3%		N.S.	Waritz, 1971
		Mice		10%				30 min.	Paulet, 1964
		Rabbit and Guinea Pig		25%				30 min.	Paulet, 1964
		Guinea Pig					10%	2 hr.	Clayton, 1966
CCl_2F_2	F-12	Rats, Guinea Pigs and Rabbits		>80%				30 min.	Paulet, 1969
		Rats					80%	4-6 hrs.	Lester and Greenburg, 1950
		Mice		76%				30 min.	Paulet, 1969
		Rats			50%			1 hour	Keubler, 1964
		Higher Vertebrates (N.S.)			40%			N.S.	Caujolle, 1964
		Rats				30-40%		N.S.	Lester and Greenburg, 1950
		Dogs, Monkeys and Guinea Pigs					20%	Prolonged	Sayers *et al.*, 1930
		Guinea Pig					20%	2 hr.	Clayton, 1966
F-11/F-12 (1:1,v/v)	-	Mice		22%				30 min.	Paulet, 1969
		Rats		30%				30 min.	Paulet, 1969
		Guinea Pig		50%				30 min.	Paulet, 1969
$CClF_3$	F-13	Guinea Pig					20%	2 hr.	Clayton, 1966
CF_4	F-14	N.S.					20%	2 hr.	Zapp, no date

Table L. Acute Inhalation Toxicity of Halo-unsaturated Methanes in Laboratory Animals

Fluorocarbon	Code	Animal	ALC	LC_{50}	Anesth.	Tremors	Non-lethal	Duration	Reference
$CHCl_2F$	F-21	Guinea Pig	5%					<2 hr.	Caujolle, 1964
			10%					1 hr.	Clayton, 1966
		Higher Vertebrates	10%					brief	Caujolle, 1964
					1-2%			several minutes	Caujolle, 1964
$CHClF_2$	F-22	Guinea Pigs				10%		2 hr.	Waritz, 1971
							20%	2 hr.	Caujolle, 1964
		Dogs	70%		40%			<90 min.	Van Poznak and Artusio, 1960
		Mice	40%					2 hr.	Clayton, 1966
CHF_3	F-23	Rat					20%	2 hr.	Zapp, no date
		Dogs					80%	<90 min.	Van Poznak and Artusio, 1960

Table LI. Acute Inhalation Toxicity of Perhaloethanes in Laboratory Mammals

Fluorocarbon	Code	Animal	ALC	LC_{50}	Anesth.	Tremors	Non-lethal	Duration	Reference
CCl_2F-CCl_2F	112	Rat	1.5%					4 hr.	Clayton et al., 1964
		Rat	3% [severe pulmonary hemorrhage]					40-60 min.	Greenburg and Lester, 1950
			0.5% [delayed death, 18-36 hrs.]					18 hr.	
CCl_3-CClF_2	112a	Rat	1.5%					4 hr.	Clayton et al., 1964
			2-3%					1½-2½ hr.	Greenburg and Lester, 1950
$CF_2Cl-CFCl_2$	113	Rat	5.5%					4 hr.	Waritz, 1971
			8.69%					4 hr.	Clayton, 1966
			10%					4 hr.	DuPont, S-24, no date
			20%					45 min.	Kuebler, 1964
				11% [some delayed death <2 hr.]				2 hr.	Desoille et al., 1968
		Mice		>10%				30 min.	Raventos and Lemon, 1965
		Mice		9.5%				2 hr.	Desoille et al., 1968
		Mice and Rats			15%			15 min.	Kuebler, 1964
		Mice			5.7% [delayed death with >6%]			30 min.	Raventos and Lemon, 1965
		Rats				2.5-2.9%		30 min.	DuPont, S-24, no date
							1.1%	6 hrs.	Steinberg et al., 1969
		Guinea Pig	4.8-5.2%					1 hr.	DuPont, S-24, no date
				12%				2 hr.	Desoille et al., 1968
		Dog				1.1%		6 hr.	Steinberg et al., 1969
						1.3%		1 hr.	Steinberg et al., 1969
$CClF_2-CClF_2$	F-114	Rats	60%					2 hr.	Waritz, 1971
					50%			2 hr.	Kuebler, 1964
		Mice		70% [delayed death <24 hrs.]				30 min.	Paulet and Desbrousses, 1969
		Dogs				20%		2-5 min.	Yant et al., 1932
		Guinea Pig					20%	9 hr.	Yant et al., 1932
		Mice	[10%:alveolar hemorrhage]					24 hr.	Quevauviller et al., 1953
CF_3-CFCl_2	114a	Mice		70% [delayed death, <2 hrs.]				30 min.	Paulet and Desbrousses, 1967
		Rat	72%					30 min.	Paulet, 1969
		Rabbit	75%					30 min.	Paulet, 1969
		Rats	20% [delayed death]					N.S.	Caujolle, 1964
CF_3-CClF_2	115	Rats					80%(20% O_2)	4 hr.	Clayton, 1966
CF_3-CF_3	116	Rats					80%(20% O_2)	N.S.	Caujolle, 1964
F-22/F-115	F-502	Rats	[20% = pulmonary congestion]					N.S.	Caujolle, 1964

Table LII. Acute Inhalation Toxicity of Halo-unsaturated Ethanes in Laboratory Mammals

Fluorocarbon	Code	Animal	ALC	LC_{50}	Anesth.	Tremors	Non-lethal	Duration	Reference
CF_2Cl-CH_2Cl	F-132	Mice		1.3%	1.3% [delayed death in 24-48 hrs.]			10 min.	Robbins, 1946
		Mice		4.9%	1.29% [no delayed death noted in 15 days]			30 min.	Raventos and Lemon, 1965
		Rabbits					3% [lung lesions]	N.S.	Raventos and Lemon, 1965
$CClF_2-CH_3$	F-142b	Mice	12.8%					4 hr.	Carpenter *et al.*, 1949
					20%			N.S.	Lester and Greenburg, 1950
CHF_2-CH_3	F-152a	Rats	50-55%					10-25 min.	Lester and Greenburg, 1950
					<45%			N.S.	Lester and Greenburg, 1950
			6.4%					4 hr.	Carpenter *et al.*, 1949
CF_3-CHCl_2	F-123a	Mice		7.6%				30 min.	Raventos and Lemon, 1965
				7.7%				10 min.	Robbins, 1946
					2.4%			30 min.	Raventos and Lemon, 1965
					2.7%			10 min.	Robbins, 1946
$CClF_2-CHClF$	F-123	Dog			7%	none		15 min.	Burn, 1959
		Mice			4%	none		30 min.	
							7%	1 hr.	
CF_3-CH_2Cl	F-133			25%	8%			10 min.	Robbins, 1946
				15%	4.3%			30 min.	Raventos and Lemon, 1965
CF_3-CH_3	F-143	Mice		50%				10 min.	Robbins, 1946
$CClF_2-CHF_2$	F-124	Guinea Pig					20%	2 hr.	Clayton, 1966
$CF_3-CHClF$	F-124a	Dog			40%			2 min.	Van Poznak and Artusio, 1960
CHF_2-CF_3	F-125	Rats					10%	4 hr.	Clayton, 1966
		Dog	[90%=long lasting excitement stage]					rapid onset	Van Poznak and Artusio, 1960

Table LIII. Acute Inhalation Toxicity of Bromofluoromethanes in Laboratory Mammals

Fluorocarbon	Code	Animal	ALC	LC_{50}	Anesth.	Tremors	Non-lethal	Duration	Reference
CCl_2FBr	H-1121	Mice		~2%				30 min.	Raventos and Lemon, 1965
					2%			30 min.	Raventos and Lemon, 1965
CF_2Br_2	H-1202	Rat	5.5%					15 min.	Clayton, 1966
$CClF_2Br$	H-1211	Rat	30%					15 min.	Beck et al., 1973
			30-32%					15 min.	Clark, 1972
			23%					30 min.	Clark, 1972
		Mice and Rats				6%		12 min.	Beck et al., 1973
		Rat					25%	30 min.	Caujolle, 1964
		Guinea Pig	23%					15-30 min.	Clark, 1972
						6%		21 min.	Beck et al., 1973
		Dog				5%		3 min.	Beck et al., 1973
		Monkey				7.8%		10 min.	Beck et al., 1973
CF_3Br	H-1301	Rat	83.2% [in O_2]					15 min.	DuPont, S-35A, 1971
		Mice and Rats	80% [in O_2]					30 min.	Caujolle, 1964
		Mice and Guinea Pigs	85% [in O_2][delayed death, 2 days]					2 hr.	Paulet, 1962
		Dogs				20%		1-3 min.	Van Stee and Back, 1969
		Mice, Rats, Rabbits and Guinea Pigs					90% [in O_2]	N.S.	Paulet, 1962

Table LIV. Acute Inhalation Toxicity of Bromofluoroethanes in Laboratory Mammals

Fluorocarbon	Code	Animal	ALC	LC_{50}	Anesth.	Tremors	Non-lethal	Duration	Reference
CH_2Br-CF_2Br	H-2202	Rats	0.5%					18 hr.	Lester and Greenburg, 1956
					0.25%			18 hr.	Lester and Greenburg, 1950
$CH_2Br-CHF_2$	H-2201	Rats		4.6%	1.3%			10 min.	Robbins, 1946
$CHBr_2-CF_3$	H-2302	Mice	1.2%		0.5%			30 min.	Raventos and Lemon, 1965
		Mice	2.0%		0.4%			10 min.	Robbins, 1946
CH_2Br-CF_3	H-2301	Mice		9.76%	2.51%			30 min.	Raventos and Lemon, 1965
				11.7%	2.8%			10 min.	Robbins, 1946
$CBrF_2-CBrF_2$	H-2402	Rats	17.3%					4 hr.	Rainaldi, 1972
							13.1	4 hr.	Rainaldi, 1972
$CHBrF-CF_3$	H-2401	Dogs			25%			rapid	Van Poznak and Artusio, 1960

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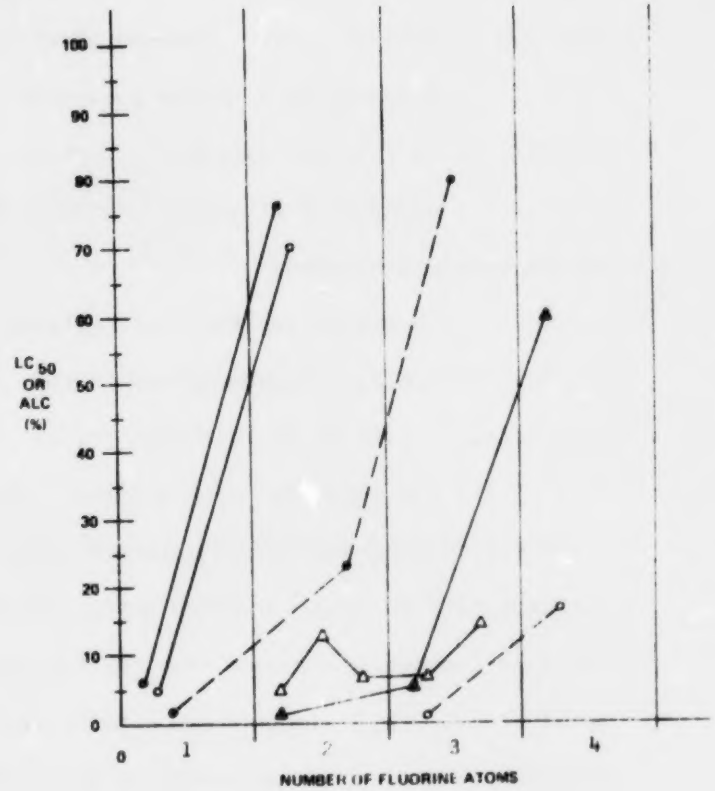

DATA FROM	1	2	3	4
TABLE IL. PERHALOMETHANES ●——●	CCl_3F	CCl_2F_2		
TABLE L: HALO-UNSATURATED METHANES ○——○	$CHClF_2$	$CHCl_2F$		
TABLE LI: PERHALOETHANES ▲——▲		CCl_2F-CCl_2F	$CFCl_2-CClF_2$	$CClF_2-CClF_2$
TABLE LII: HALO-UNSATURATED ETHANES △——△		132, 142b, 152a	CF_3-CHCl_2 CF_3-CH_2Cl	
TABLE LIII: BROMOFLUOROMETHANES ●– – – –●	CCl_2FBr	CF_2ClBr	CF_3Br	
TABLE LIV: BROMOFLUOROETHANES ○– – – –○			$CHBr_2-CF_3$	$CBrF_2-CBrF_2$

Figure 26: Comparative Toxicity of Various Fluorocarbons

Similar relationships showing increasing potency with decreasing fluorination can be made in other responses given in Tables IL-LIV.

Although most of the published information on acute inhalation toxicity is in relative agreement, certain studies warrant further elaboration either because of unresolved details or information that could not be adequately tabulated.

In evaluating the toxic effects of F-112 (CCl_2F-CCl_2F) and F-112a (CCl_3-CClF_2), Greenburg and Lester (1950) noted that both compounds were fatal to rats at 3%, although F-112a caused death in 1-2 1/2 hours while F-112 was fatal in 40-60 minutes. However, the primary difference noted was varying degrees of pulmonary hemorrhage caused by F-112 which were not seen in F-112a exposed rats. Clayton and coworkers (1964), using the same compounds, exposed rats for four hours and noted an ALC of approximately 1.5%. While unspecified effects were observed on the nervous and respiratory system, no pathology is reported.

Fluorocarbon-113 ($CCl_2F-CClF_2$) has been rather extensively studied for acute inhalation toxicity. Although lethal concentrations range between 5.5-20%, a two-hour exposure to 1.76% was associated with moderate liver and kidney congestion in rats, while causing no loss of coordination. A similar exposure to 3.91% F-113 did cause loss of coordination and pathological examination showed pale kidney and liver with some fatty deposition. A ten-minute exposure to 5.09% caused similar loss of coordination and pathological examination revealed mild liver congestion and pale kidneys with focal necrosis (DuPont, S-34, no date).

Similar pathological data has not been reported and the rapid reversibility of adverse effects on exposure termination has been emphasized (Steinberg et al., 1969). This is also noted by Desoille and coworker (1968) who, however, also noted periods of torpor persisting several hours after exposure to higher concentrations (≈10%). These investigators further observed delayed death up to two hours following exposure and, in two animals, delayed death during the following week. This information is, of course, equivocal. The data presented do not offer conclusive proof that the fluorocarbon exposure actually caused the pathological observations or the delayed death. However, delayed death may suggest that a metabolite rather than the parent compound may be the toxic agent (Truhaut et al., 1972). Metabolites would also be consistent with liver damage. Both Yant and coworkers (1932) and Paulet and Desbrousses (1969) noted similar delayed death with F-114 in dog at 20% and mice at 50% concentration. With Yant and coworkers (1932), one dog died 69 hours after exposure and another died 7.3 days after 16 hours of exposure to 20% F-114. Pathological findings included moderate to marked congestion of lungs with areas of hemorrhage, very marked congestion of the liver, and congested kidneys with pale yellowish granular cortex.

The central nervous system effects of acute fluorocarbon exposure have been most extensively studied for H-1301 ($CBrF_3$). In terms of lethality, this compound is among the least toxic of the fluorocarbons with ALC's ranging from 80-85% in oxygen (see Table LIII). Paulet (1962) noted fatality in mice and guinea pigs at concentrations of 80% H-1301 (in 20% O_2). Both guinea pigs and rats responded to ten-minute exposures with general instability, difficulty in walking, and lethargy. Mice showed greatly reduced activity, more severe instability, tremors, and labored breathing. Rabbits responded the most severely with protruding eye balls, extreme dialation of the pupils, tremors, and brief convulsions. Rhoden and Gabriel (1972), however, noted a much more severe response in Westar rats at concentrations of 79% H-1301 (21% O_2), consisting of convulsions followed by respiratory arrest within 40 minutes of exposure. Van Stee and Back (1969) noted species differences between monkeys and dogs. Dogs, exposed to 50-80% H-1301 for 3-12 minutes, had epileptiform convulsions of 10-30 seconds duration including rigidity, apnea, and cyanosis of the tongue. At lower concentrations, dogs appeared agitated and exhibited transient tremors. Monkeys, however, evidenced cortical depression, shivering, and a tranquilization of their normally aggressive behavior. In a subsequent study, Carter and coworkers (1960b) demonstrated that 20-25% H-1301 significantly impaired the performance of trained monkeys and higher concentrations completely disrupted operant behavior without signs of CNS depression or analgesia.

2. Acute Oral Toxicity

Because of their uses and physical characteristics, very little information is available on the acute oral toxicity of the fluorocarbons. Such information is briefly summarized in Table LV.

Table LV. Acute oral toxicity of various fluoroalkanes in rats
(Clayton, 1966)

Fluorocarbon	Code	ALD, mg/kg
CCl_2F_2	F-12	>1,000[+]
$CHCl_2-CClF_2$	F-122	7,500
CCl_2F-CCl_2F	F-112	25,000
$CClF_2-CCl_3$	F-112a	25,000
$CClF_2-CCl_2F$	F-113	45,000 (LD_{50} = 43,000)
$CClF_2-CClF_2$	F-114	>2,250[+]

[+] = Maximum feasible dose of fluorocarbon dissolved in peanut oil.

With the exception of a slight increase in liver weight at 25,000 mg/kg $CClF_2-CCl_3$, no histological findings are noted by Clayton (1966) for these exposures.

Michaelson and Huntsman (1964) determined the acute oral toxicity of F-113 in Sprague-Dawley male rats and arrived at the same figures as those presented by Clayton (1966)--i.e. ALD = 45 g/kg, LD_{50} = 43 g/kg. The details of Michaelson and Huntsman's study are given below. (See Table LVI).

Table LVI. Acute Oral Toxicity of F-113 in Rats
(Michaelson and Huntsman, 1964)

Animal group	Dose, mg./kg.	Mortality / total animals	Approx. time of death	Av. wt. change at death, g.	Av. wt. change of survivors, g.
1	30	0/5		...	+46
2	35	0/5		...	+41
3	40	0/5		...	+19
4	45	3/5	5 to 24 hr.	-12	+25
5	50	4/5	1 to 7 days	-49	+31
6	55	5/5	3 to 9 days	0	...

The more rapid onset of death from lower lethal concentrations is noted but no explanation is offered by the original investigators. Survival seems to be related to weight maintenance but the mechanism involved is not clear. All animals were reported to have liquid fecal discharge but increased frequency of discharge is not noted. Significant pathological findings in fatally exposed animals include hemorrhage in the lungs and mottled surface but not discolored livers. Surviving animals showed only slight lung hemorrhage at higher exposures. Introduction of 200 ml (302g) F-113 into the stomachs of two dogs for two hours resulted in no gross histological change.

Fluorocarbon-11 (CCl_3F) was intubated into albino female rats at doses of 7.38 g/kg (Slater, 1965). Tests at three and twenty-four hours after exposure showed normal serum beta-glucuronidase and, after one hour, levels of liver NADP and $NADPH_2$ were also normal. Histological examination of the liver at three and twenty-four hours failed to show any necrosis. No fatalities were noted.

3. Acute Dermal Toxicity

Fluorocarbon-112 and F-112a have been applied on the skin of rabbits at doses of 7.5 g/kg and 11 g/kg, respectively (the highest feasible doses). Although no fatalities resulted, F-112 did cause skin erythema but no systemic or histological effects. Fluorocarbon-112a caused severe skin irritation in ethanol, weight loss, and histological changes in skin musculature. Guinea pigs responded similarly to F-112 with mild irritation but no sensitization.

Fluorocarbon-113 ($CCl_2F-CClF_2$) produced only local irritation when applied at 11 g/kg to the skin of rabbits.

Fluorocarbon-114 produced no irritation when sprayed directly on the backs of guinea pigs (Clayton, 1966).

B. Subacute Toxicity

1. Subacute Inhalation Toxicity

Defining subacute and chronic toxicity studies of the various fluorocarbons is somewhat arbitrary in that both duration of exposure (hrs/day) and the number of days on which the exposures are repeated must be considered. Most reviews do not differentiate between subacute and chronic studies (e.g. Clayton, 1966; Waritz, 1973) and, in view of the paucity of demonstrable toxic effects, this approach is justifiable. However, such classification includes such exposures as 2 hrs/day x 20 days and 8 hrs/day x 3 days along with exposures of 6 hrs/day x 300 days and 24 hrs/day x 92 days. In that most present information indicates that these fluorocarbons are rapidly eliminated from the body after terminating exposure, relatively brief exposures even when repeated over a number of days probably represent a different type of potential hazard than longer exposures repeated over comparable periods. Thus, in this review, chronic exposures will be defined as those lasting for at least 6 hrs/day [approximating occupational periods] and continued for at least 30 days. Exposures not falling in this category are classified as subacute. Using this admittedly arbitrary definition, data on subacute inhalation toxicity is summarized in Table LVII.

Table LVII. Subacute Inhalation Toxicity of Various Fluorocarbons.

Fluorocarbon	Code	Acute ALC	Animal	% (V/V) Conc.	Hr/Day	Days	Mortality	Comments	Reference
CCl_3F	F-11	6% x 4 hr.	Rats Mice G. Pigs Rabbits	0.4%	6 hr.	28	0/12 0/8 0/2 0/1	No significant signs of toxicity in any animals either after exposure or after 15 days recovery.	Clayton, 1966
			Rats	1.2%	4 hr.	10	0/4	Slight twitching, chewing motion, respiratory increase during exposure. Pathology: Brain-neuronal edema and neurolial vacuol; Liver-vacuolation of cells; Lungs-emphysema and edema; Spleen-increased hematopoiesis.	Clayton, 1966
			Dog	1.25%	3.5 hr	20	0/2	No signs of toxicity	Clayton, 1966
			Cats G. Pigs Rats	2.5%	3.5 hr	20	0/2 0/3 0/5	No signs of toxicity	Clayton, 1966
			Mice	25.0%	0.83 (bid)	1000	0/30	No signs of toxicity Total dose of 970 mg/kg/day	Smith & Case, 1973
			Dogs	24.5%	0.83 (bid)	90	0/4	No signs of toxicity Total dose of 560 mg/kg/day	Smith & Case, 1973
			Dogs	24.5%	0.83 (bid)	365	0/6	Transient drowsiness after exposure. Total dose 2240 $mg/k_g/day$	Smith & Case,

Table LVII (continued)

Fluorocarbon	Code	Acute ALC	Animal	% (V/V) Conc.	Hr/Day	Days	Mortality	Comments	Reference
CCl_2F_2	F-12	>80% Rats, G. Pigs, Rabbits	Cats	10%	3.5	20	0/2	No signs of toxicity	Clayton, 1966
			G. Pigs				0/3		
			Rats				0/5		
			Dogs				0/2		
			Mouse	48.9%	0.83 (bid)	1000	0/30	No signs of toxicity	Smith & Case, 1973
			Rat	40.0%	0.83 (bid)	93	0/16	No signs of toxicity	
			Dog	42.0%	0.83 (bid)	93	0/4	No signs of toxicity	
			Dog	50.0%	0.83 (bid)	90	0/4	No signs of toxicity	
			Dog	50.0%	0.83 (bid)	365	0/6	Occasional depression and drowsiness during exposure.	
$CClF_3$	F-13		Rats	1%	6	20	0/6	No signs of toxicity	Clayton, 1966
$CBrF_3$	F-1301	85% x 2 hr Mice & Guinea Pigs	Mice	50%	2	15	1/20	Mortality not related to exposure	Paulet, 1966
			Rats	50%	2	15	0		
			G.Pigs	50%	2	15	1/10	" " "	
$CHCl_2F$	F-21	10% x 1 hr G. Pig	Puppies	40%	5 min. (bid)	14	0/2	Sedation and ataxia during exposure	Smith & Case, 1973
$CHClF_2$	F-22	40% x 2 hr Mice	Puppies	60%	5 min. (bid)	14	0/2	Sedation and ataxia during exposure	Smith & Case, 1973
$CCl_2F\text{-}CCl_2F$	F-112	1.5% x 4 hr., Rat	Rats	0.3%	4	10	0/4	Prostrate and incoordinate during first exposure. Rapid and shallow respiration. Hyper-responsive during each exposure. Immediate recovery after exposure.	Clayton, 1966
			Rats	0.1%	18	16	0/6	No evident effect	Greenburg & Lester, 1950
$CCl_3\text{-}CClF_2$	F-112a	1.5% x 4 hr., Rat	Rat	0.1%	18	16	0/6	No evident effect	Greenburg & Lester, 1950

Table LVII (continued)

Fluorocarbon	Code	Acute ALC	Animal	% (V/V) Conc.	Hr/Day	Days	Mortality	Comments	Reference
$CCl_2F-CClF_2$	F-113	5.5% x 4 hr., Rats	Mice	1.1%	0.83 (bid)	690	0/30	No signs of toxicity.	Smith & Case,'73
			Cats	1.25%	3.5	20	0/2	No signs of toxicity	Clayton, 1966
			Dogs				0/2		
			G. Pigs	2.5%	3.5	20	0/2		
			Rabbits	1.1%	2*	120-1080	0/6	No variation from controls	Desoille *et al.*, 1968
			Rats	1.2%	2*	365-730	3/6	Deaths not associated with exposure. Slight sleepiness during exposure.	Desoille *et al.*, 1968
			Rat	0.2%	24	14	0/50	Enlarged thyroid glands in all monkeys exposed. Rat kidneys increased in weight above controls. Neither effect conclusively attributed to exposure.	Carter et al., 1970
			Mice				0/40		
			Dogs				0/8		
			Monkeys				0/4		
			Dogs G. Pigs Rats	0.51%	6	20*	0/4	No toxic effects.	Steinberg *et al*, 1969
			Rats	6%	1	5	0/5	Liver: Two rats showed fair amount of fat in Kupffer cells possibly indicative of change in lipide or lipoproteins by compound. Not definitely attributable to exposure.	Burn et al., 1959
				4%	1	5	0/4	Mildly toxic effect in liver. Moderate degree of mitotic activity in liver cell of one rat. Three others showed similar activity at a lesser degree.	

Table LVII (continued)

Fluorocarbon	Code	Acute ALC	Animal	% (V/V) Conc.	Hr/Da	Days	Mortality	Comments	Reference
$CClF_2-CClF_2$	F-114	60% r 2 hr., Rats	Cats G. Pigs Rats Dogs	10	3.5	20	0/2 0/3 0/5 0/2	No signs of toxicity	Clayton, 1966
			Mice Rats	10	2.5*	10	0/10 0/10	No signs of toxicity	Paulet & Desbrousses, 1969
			Mice Rats	20			0/20 0/10	Exudative & congested lesions of the alveoli and bronchioles without cell structure alteration. Slight decrease in equilibrium.	
			Rats	12	2.5*	30	0/30	No toxic effects	Quevauviller, *et al*., 1953.
			G. Pigs	14.16%	8	21	1/6	No signs of toxicity. Death not related to exposure. Occasional slight fatty degeneration of liver.	Yant et al., 1932
				20%	8 8	4 2	0/6 0/10	Ruffled fur and occasional convulsive jerk. Increase in excreta.	
			Dogs	14.16	8 8	3 21	0/1 0/2	Salivation and wretching. Occasional convulsions with incoordination and tremors during first three days. After this, a definite tolerance developed to exposure. Increases in hemoglobin, red blood cells, and younger forms of polymorphonuclear leucocytes.	

Table LVII (continued)

Fluorocarbon	Code	Acute ALC	Animal	% (V/V) Conc.	Hr/Day	Days	Mortality	Comments	Reference
	F-116 cont.			20	8	3-6	4/4	Same as above, but more severe Plus pathology as follows: Brain-congestion of meningeal vessels; heart-myocardium congested; liver-very marked congestion with friability in some instances; Kidneys-congested, pale yellowish glandular cortex; Gastrointestinal tract-gastric and duodenal mucosa markedly congested and swollen. One dog had suggestion of duodenal ulcer.	
			Rats	12	2*	184	2/6	Small increase in number of red blood cells in rats.	Desoille et al., 1973.
			Rabbits	12	2*	207	0/6	No signs of toxicity	" "
			Mice	25%	0.83 (bid)	690	0/30	No toxic effects	Smith & Case, 1973
			Rats	30%	0.83 (bid)	93	0/16	No toxic effects	
			Dogs	30%	0.83 (bid)	93	0/6	No toxic effects	
			Dogs	25%	0.83 (bid)	90	0/4	No toxic effects	
			Dogs	25%	0.83 (bid)	365	0/6	Occasional depression during exposure.	
[illegible]	F-142b	12.8% x 4 hr., Rats	Rats	10%	16	2-9	10/10	Extensive consolidation and hepatization of lung.	Lester & Greenburg, 1950

*Five days/week

2. Subacute Oral Toxicity

As in cases of acute exposure, the subacute and chronic oral toxicity of the fluorocarbons has not stimulated as extensive investigations as the more common route of inhalation.

Fluorocarbons F-112 (CCl_2F-CCl_2F) and F-112a ($CClF_2$-CCl_3) have been studied by both Greenburg and Lester (1950) and Clayton (1966). Rats fed 2 gm/kg/day of either compound for 23 to 33 days exhibited no signs of toxicity and no pathological changes in any organs (Greenburg and Lester, 1950). At concentrations of 5g/day for ten days, both compounds caused tremors, inactivity, initial weight loss, diahrhea, and slight increase in liver weight. In addition, F-112 caused slight reversible histological change in the liver (Clayton, 1966).

Similar to the above compounds, fluorocarbon 114 is tolerated by rats at doses of 2g/kg/day for 23-33 days (Quevauviller, 1964).

Fluorocarbon 115 has also been tested at concentrations of 140-172 mg/kg/day for ten days (five days a week for two weeks). No evidence of toxicity was found either immediately or ten days after exposure (Clayton, 1966).

3. Subacute Dermal Toxicity

Fluorocarbon-113 (CCl_2F-$CClF_2$) applied to rabbit's skin at 5g/kg/day for five days caused gross and histological damage to the skin as well as slight changes in the liver (Clayton, 1966). Fluorocarbon-11, F-12, F-113, and F-114 at 40% in sesame oil have been sprayed onto shaved rabbit skin for twelve exposures with no effect. Severe local irritation is produced by F-113 at 5g/kg/day on shaved rabbit skin after five days. In this instance, however, the sprayed surface was covered for two hours after each application (Waritz, 1973).

C. CHRONIC TOXICITY

1. Chronic Inhalation Toxicity

Similar to information presented on subacute exposure in Table LVII, Table LVIII summarizes the work of various investigators on chronic exposures.

Jenkins and coworkers (1970), as indicated in Table LVIII, studied the chronic toxicity of F-11 in rats, guinea pigs, rabbits, and monkeys with exposures of 1.025% x 5 days/week x 6 weeks and 0.1% x 24 hrs/day x 90 days. Only one animal died, a monkey used in the continuous exposure, showing hemorrhagic lesions on the surface of the lung that was not directly attributed to inhalation. In monkeys surviving continuous exposure, a large amount of inflamatory infiltration was noted, occasionally associated with microfilarial parasite infestation. Blood smears of half of all monkeys, both experimental and control, showed such parasites. Nonspecific inflamation of the lungs was evident in all experimental species except dogs used in repeated exposure. Such changes were not described for control animals. Mild discoloration was noted in the livers of one-fourth of the rats and guinea pigs in both exposures. A 2 x 4 mm liver lesion was noted in one of the male rats from the continuous exposure. Of eight rats examined after repeated exposures, one evidenced focal myocytolysis and two showed focal nonspecific myocarditis. The investigators did not relate these changes to F-11 exposure. Marked increases in serum urea nitrogen were noted in dogs exposed continuously (33 mg/100 ml) and repeatedly (36 mg/100 ml) [control = 16.8 mg/100 ml]. This was not noted in any other animals tested.

Table LVIII. Chronic Inhalation Toxicity of Various Fluorocarbons

Fluorocarbon	Code	Acute ALC	Animal	% (V/V) Conc.	Hr/Day	Days	Mortality	Comments	Reference
CCl_3F	F-11	6% x 4 hr. Rats	Rats G. Pigs Dogs Monkeys	1.025%	8	30	0/15 0/15 0/2 0/9	No outward signs of toxicity. See text for detailed discussion.	Jenkins, et al. 1970
			Rats G. Pigs Dogs Monkeys	0.1%	24	90	0/15 0/15 0/2 1/9	Hemorrhagic lesions on surface of lung not directly attributable to compound.	
CCl_2F_2	F-12	80%, Rats, G. Pigs, Rabbits	Dogs Monkeys G. Pigs	20% 20% 20%	7-8 7-8 7-8	52 35-52 35-56	0/2 0/2 10/26	Dogs and monkeys apparently developed tolerance to exposure, tremors disappearing after first two weeks. Deaths in Guinea pigs not related to exposure. See text for more detailed discussion.	Sayers et al., 1930
			Rats G. Pigs Rabbits Dogs Monkeys	0.0840%	8*	30	2/15 1/15 0/3 0/2 0/3	Guinea Pigs--several showed focal necrosis or fatty infiltration of liver. Monkey-heavy pigment deposits in liver, spleen, and kidney.	Prendergast et al., 1967
			Rats G. Pigs Rabbits Dogs Monkeys	0.0810%	24	90	1/15 0/15 0/3 0/2 0/3	Guinea pigs-all showed slight to extensive fatty infiltration of liver and several had focal or submassive necrosis of liver (see text).	
$CHClF_2$	F-22	70%, Rats	Rabbits Rats Mice	1.42	6	300	N.S. N.S. N.S.	see text	Clayton, 1966
			Rats Mice	0.198%	6	300	N.S. N.S. N.S.	No toxic effects	Clayton, 1966
$CBrF_3$	H-1301	85% x 2 hr. Mice & Guinea Pigs	Rats	2.3%	6	90	0/30 0/3	No signs of toxicity	Clayton, 1966
CCl_2F-CCl_2F	F-112	1.5% x 4 hr., Rats	Rats Mice G. Pigs Rabbit	0.1%	6	31	0/16 0/10 0/2 0/1	Female rats (8): significant decrease in leukocyte count. Male Rats: liver and kidney weights greater than control. Transient liver reactions in rats.	Clayton, 1966
$CCl_2F-CClF_2$	F-113	5.5% x 4 hr., Rats	Rats	0.0252%	7	30	0/21	No signs of toxicity	Clayton, 1966
			Rats	0.5%	7	30	0/12	Three rats showed slightly pale livers.	Clayton, 1966
$CClF_2-CF_3$	F-115	80% x 4 hr., Rats	Rats Mice Rabbits Dogs	10%	6*	90	0/20 0/10 0/4 0/4	No signs of toxicity	Clayton et al., 1966
CH_3-CHF_2	F-152a	6.4% x 4 hr., Rats	Rats	10%	16	60	0/8	No signs of toxicity. Mild chronic irritation of lungs in five rats.	Lester & Greenburg, 1950
CH_3-CClF_2	F-142a	12.8% x 4 hrs., Rats	Rats	1%	16	60	0/[illegible]	No signs of toxicity. Mild chronic irritation of lungs in two rats.	Lester & Greenburg, [illegible]

* = 5 days/week

Sayers and coworkers (1930) exposed dogs, monkeys, and guinea pigs to CCl_2F_2 at 20% for 7-8 hrs/day for periods of 35-52 days in most cases. Ten of the twenty-six guinea pigs died during the test. These deaths, however, were associated with handling procedures and not to fluorocarbon exposure. During the first couple of weeks, dogs and to a lesser extent guinea pigs developed tremors and ataxia during exposure. The subsidence of these effects seemed to indicate a tolerance to F-12 exposure. Guinea pigs did not have these signs. Also, during the first two or three weeks, a slight to moderate weight loss was noted along with an increase in red blood cell count and hemoglobin. Differential leucocyte count showed a slight decrease in lymphocytes and an increase in polymorphonuclear neutrophils. No variations from controls in frequency of pregnancy and bearing healthy young was noted in exposed guinea pigs.

Prendergast and coworkers (1967) did note liver damage in guinea pigs on both repeated and continuous exposures to F-12 at concentrations below the TLV (1000 ppm). This effect does seem related to exposure in that the severity of the affect increased in continuous as opposed to repeated exposures. In referring to a study indicating that guinea pigs are particularly susceptible to liver damage and fatality when exposed to mineral spirits (Rector et al., 1966), Prendergast and coworkers (1967) do not definitely attribute the liver necrosis to F-12. However, it should be noted that Rector and coworkers (1966), although recognizing that liver damage and death may not be indicators of occult toxicity, do conclude that the guinea pig is the best rather than an unsuitably susceptible test animal in setting guidelines on long-term low level exposure.

Clayton (1966) referenced a study by Karpov (1963) exposing rabbits, rats, and mice to 1.42% F-22 for 6 hrs/day x 10 months. Mice showed lower endurance in a swimming test and an increase in the number of trials needed to establish a conditioned reflex. Rats showed a decrease in oxygen consumption and an increase in subthreshold stimuli needed to induce a response. Rabbits showed decreases in red blood cell count, hemoblobin, lymphocytes, reticulocytes, blood cholinesterase, and serum albumin and increases in neutrophiles, eosinophiles, and globulin. Pathological examination revealed degenerative changes in heart, liver, kidney, and nervous system as well as changes in lungs leading to emphysema and exudate alveolar septal thickening.

2. Chronic Oral Toxicity

Fluorocarbon-12 is the only compound studied in which chronic oral toxicity studies have been obtained: Studies of F-11 and F-114 have also been recently completed (Waritz, 1973).

Waritz (1973) summarizes the results of a 90-day feeing study with rats at doses of 35 and 350 mg/kg/day and dogs at doses of 10 and 100 mg/kg/day. No deviations are noted from either control groups except that rats had elevated but not abnormal levels of urinary fluoride and plasma alkaline phosphatase.

Sherman (1974) has conducted a two year feeding study in rats using doses of 15 and 150 mg/kg/day. At the higher concentration, a rate of body weight gain was decreased in both male and female rats (see Fig. 27).

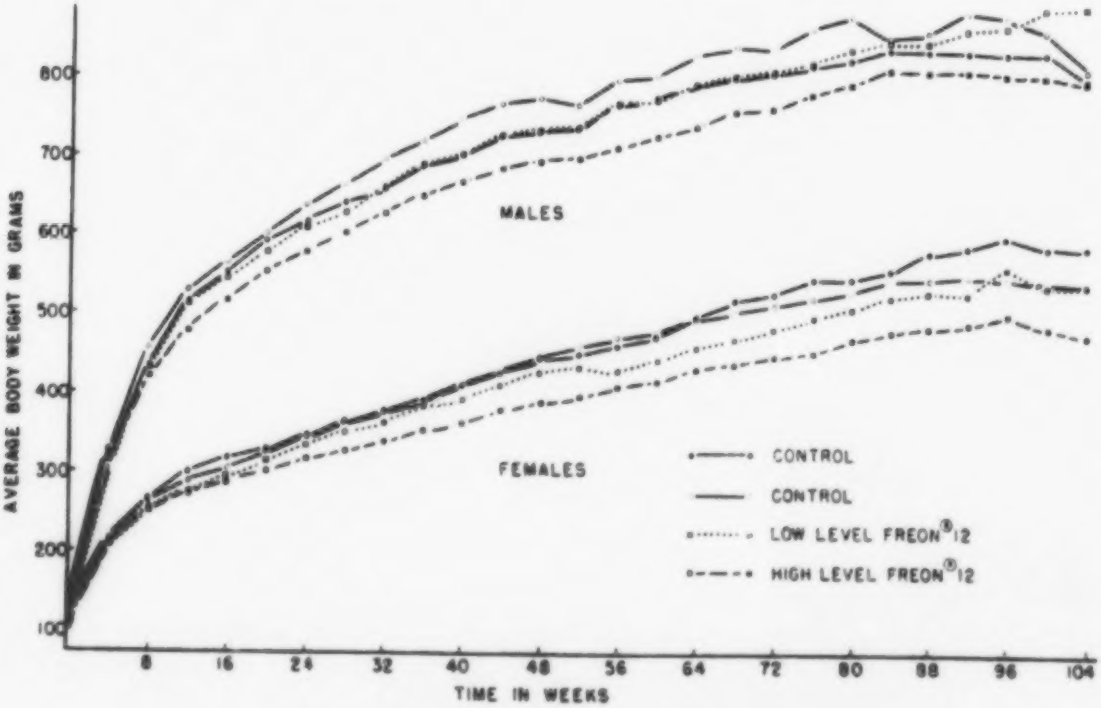

Figure 27. Growth of Male and Female Rats
Orally Administered F-12
(Sherman, 1974):
reprinted with permission from DuPont deNemours Co.

A slight decrease was noted in the food use efficiency (g. wgt. gained/g. food consumed) of female rats at the higher dosage level and this seems to be reflected in growth curves. Levels of elevated urinary fluoride were not noted. Other parameters tested - including liver function, hematology, and histopathology - were normal.

3. Chronic Dermal Toxicity

Fluorocarbon-113 ($CC\ell_2F-CC\ell F_2$) has been applied to the shaved back of rabbits five times a week for twenty weeks with no visible adverse affects (Desoille et al., 1968).

Quevauviller and coworkers (1964) and Quevauviller (1965) have applied F-11 ($CC\ell_3F$), F-12 ($CC\ell_2F_2$), F-112, and mixtures of F-11 and F-12, and F-11 and F-22 to the skin, tongue, soft palate, and auditory canal of rats 1-2/day x 5 days/week x 5-6 weeks. Each compound was sprayed on the surface forfive or ten seconds from a distance of 10-20 cm. Slight irritation was noted in the skin and no significant effects in the other areas. However, the healing rate of burns was noticeably retarded by all of the compounds as indicated in Table LIX.

Table LIX. Per Cent Reduction of the Surface of Burns in Control Rats and Burns Sprayed with Various Fluorocarbons (Quevauviller, 1965)

Days	Control	F-11	F-12	F-11 + F-12	F-11 + F-22	F-114
4	31	0	0	6.8	5	+ 6
6	48	2.8	14	17	36	+14
8	65	14	21	24	55	3
12	80	30	50	65	79	57
14	87	48	71	69	92	68
18	100	87	100 ?	89	100 ?	82

D. Cardiovascular Effects of Fluorocarbons

1. Cardiac Sensitization to Exogenous Epinephrine Induced Arrhythmias

Epinephrine, a catecholamine, is a potent adrenal cortical hormone. In man, the mean blood plasma concentration is approximately 0.06 µg/ℓ and excesses are eliminated rapidly from the body, primarily through O-methylation. In stress, the human adrenal gland may secrete 0.004 mg/kg/min. The compound has a variety of cardiovascular effects, chief of which are vasoconstriction - resulting in increased blood pressure - and increases in both heart rate and cardiac output. A variety of hydrocarbons, with and without halogen substitution, have long been known to sensitize the heart to epinephrine induced arrhythmias including ventricular fibrillation (Garb and Chenoweth, 1948; Hays, 1972; Reinhardt et al., 1973). At various concentrations, fluorocarbons used for aerosol propellants, solvents and fire extinguishing agents have been shown to produce this effect. Because this arrhythmogenic action may be related to a variety of human health hazards--e.g. bronchodilator nebulizer over-use by asthmatics, "aerosol sniffing syndrome", exposures to high concentrations of fire extinguishing agents [see Section XI , Human Toxicity] - a great deal of research has been stimulated in this area focused primarily on determining the minimum concentration of fluorocarbons and epinephrine required to produce arrhythmias in various mammals.

Reinhardt and coworkers (1971) have detailed what has been the most common procedure for testing the ability of various fluorocarbons to sensitize the heart to injected doses of epinephrine. The basic procedure is outlined in Table LX.

Table LX: Outline of a procedure for determining the ability of various vapors to sensitize the heart to exogenous epinephrine-induced arrhythmias (Reinhardt et al., 1971)

Minutes	Conditions
0	Allow animal to breathe normal air.
2	Inject I.V. with dose of epinephrine in normal saline over nine seconds (control injection).
7	Expose to known concentration of gas.
12	Re-inject with epinephrine (challenge injection).
17	Discontinue exposure to gas.

In most experiments, the animals are not anesthetized and all gases - including normal air - are administered through a face mask. The standard exposure period is five minutes and ECG recordings, generally lead II, are continuous. By far the most critical parameter, however, is the dosage of epinephrine administered, since in sufficient quantity this compound alone may induce arrhythmias. Reinhardt and coworkers (1972), in formulating their protocol, found that most previous investigators used between 0.004-0.04 mg/kg, the usual amount being 0.01 mg/kg. Because this type of experiment is designed to simulate conditions of stress, the rate at which the compound is administered is probably more important than the total dose. The relevant data on epinephrine administration for the series of experiments to determine the effects of fluorocarbon cardiac sensitization is given in Table LXI.

Table LXI. Epinephrine dosage used in determining the effect of fluorocarbons in cardiac sensitization to exogenous epinephrine#

Epinephrine Dose	Duration of Administration	Rate of Epinephrine Injected	Author
0.008 mg/kg	9 seconds	0.053 mg/kg/min.	Reinhardt *et al.*, 1971 Reinhardt *et al.*, 1973 Mullin, 1970
0.01 mg/kg¶	25-40 seconds	0.015-0.024 mg/kg/min.	Reinhardt and Reinke, 1972 Burgison *et al.*, 1955
0.007 mg/kg*ϕ	2 minutes	0.0035 mg/kg/min.	Wills (1972)
0.005 mg/kg	2 minutes	0.0025 mg/kg/min.	Wills (1972)
0.010 mg/kg	2 minutes	0.005 mg/kg/min.	Wills (1972)
0.015 mg/kg	2 minutes	0.0075 mg/kg/min.	Wills (1972)
0.005 mg/kg	10 seconds	0.030 mg/kg/min.	Clark & Tinston, 1972
0.10 mg/kg*	not spec.		Van Stee and Back, 1969
0.002-0.003 mg/kg	not spec.		Van Stee and Back, 1969
0.003-0.004 mg/kg◆	not spec.		Van Stee and Back, 1969
0.010 mg/kg^{x} (I.M.)	--	--	Call, 1972
0.005 mg/kg†	10 seconds	0.030 mg/kg/min.	Beck *et al.*, 1973 *

#-Dogs, unless otherwise specified
¶-Dogs and cats
ϕ-Dogs and guinea pigs
†-Dogs and rabbits
x-rats
◆-monkey
*-concentration used in all experiments but those designed to study dose-response of epinephrine.

5 µg/kg/min. released by dogs during conditions of max. emotional stress - Satake, 1955.

The rationale for these doses is two-fold. First, within the experimental framework, they should represent doses which will not elicit serious cardiac arrhythmias: this is determined by the control injection. Secondly, in terms of applicability to hazard assessment, they should approximate or exceed the endogenous output under conditions of stress. The results obtained by the various investigators for a wide range of one and two carbon fluorocarbons are summarized in Table LXII.

Although the results of the various investigators are in relative agreement as to the concentrations of the fluorocarbons in inhaled air necessary to cause arrhythmias, the other parameters which influence these results must be fully appreciated. The most important of these are the amount of epinephrine used and duration of exposure to the fluorocarbons.

The effect of epinephrine dosage on cardiac response to a 0.87% F-11 over varying durations of exposure has been demonstrated by Wills (1972) (see Figure 28).

As would be expected, increasing the amount of injected epinephrine increases the arrhythmic response. This is consistent with the earlier work of Van Stee and Back (1969) who used epinephrine concentrations of 2-10 ug/kg. The control level sensitization five minutes after exposure to F-11 is terminated reflects the rapid elimination of the compound from the body. Similar observations of rapid loss to sensitization have been made by Clark and Tinston (1972 a and b). However, Wills (1972) notes that maximum sensitization occurs after ten minutes exposure to F-11 and falls off sharply thereafter. This decrease in response from the ten minute exposure injection to the fourteen minute exposure injection cannot be explained on the basis of other time-response studies.

Table LXII. Cardiac responses of mammals exposed to fluorocarbons and challenge injections of epinephrine

Compound	No.	Animal	V/V Conc. %	Duration Min.	No. Animals Tested	No. Sensitized	% Sensitized	Reference
METHANES								
CCl_3F	F-11	Dogs	.09-.13	5	12	0	0.0	5
			.32	5	6	0	0.0	4
			.35-.61	5	12	1	8.3	5
			.63	5	6	0	0.0	4
			.96-1.21	5	12	5	41.7	5
			1.25	5	6	3	50.0	4
		Guinea Pig	.87	15	6	6	100.0	9
CCl_2F_2	F-12	Dogs	2.0	5	6	0	0.0	4
			2.5	5	12	0	0.0	5
			4.0	5	6	0	0.0	4
			5.0	5	12	5	41.7	5
			6.0	5	6	3	50.0	4
$CHClF_2$	F-22		2.5	5	12	0	0	5
			5.0	5	12	2	16.6	5
ETHANES								
$C_2Cl_3F_3$	F-113	Dogs	.25-.27	5	12	0	0.0	6
			.40-.57	5	29	19	65.5	6
			.90-.95	5	4	3	75.0	6
$CClF_2$-$CClF_2$	F-114	Dogs	2.5	5	12	0	0	5
			2.5	5	6	0	0	4
			5.0	5	12	7	58.3	5
			5.0	5	6	0	0	4
			10.0	5	6	3	50.0	4
CF_3-$CClF_2$	F-115	Dogs	15	5	13	1	7.7	5
			25	5	12	4	33.3	5
C_2F_6	F-116	Dog	2.2	15	4	2	50.0	8
		Guinea Pig	2.2	15	10	2	20.0	9
			8.7	15	3	2	66.6	8
			15.0	15	4	4	100.0	8
$CClF_2$-CH_3	F-142b	Dog	2.5	5	6	0	0.0	4
			5.0	5	12	5	41.7	5
			10.0	5	12	12	100.0	5
CHF_2-CH_3	F-152a	Dog	5.0	5	12	0	0.0	5
			15.0	5	12	3	25.0	5
F-22/F-115	F-502	Dog	5.0	5	6	0	0.0	4
			10.0	5	12	5	41.7	5
			20.0	5	12	12	100.0	5

Reference key:

1. Beck *et al*., 1973
2. Burgison *et al*., 1955
3. Call, 1972
4. Clark and Tinston, 1972
5. Reinhardt *et al*., 1971
6. Reinhardt *et al*., 1973
7. Reinhardt and Reinke, 1972
8. Van Stee and Back, 1969
9. Wills, 1972

Table LXII
(Continued)

Compound	No.	Animal	V/V Conc. %	Duration Min.	No. Animals Tested	No. Sensitized	% Sensitized	Reference
ETHYLENES								
$CF_2=CF_2$		Dog	25-50	5-15	4	0	0.0	2
		Cat	25-50	5-15	2	0	0.0	2
$C_2H_2F_2$		Dog	25-50	5-15	8	0	0.0	2
		Cat	25-50	5-15	2	0	0.0	2
C_2ClF_3		Dog	25-50	5-15	4	4	100.0	2
C_2HClF_2		Dog	25-50	5-15	4	4	100.0	2
C_2Cl_3F		Dog	25-50	5-15	2	2	100.0	2
Bromo-ou substituted								
$CBrF_3$	H-1301	Dog	2.2	15	4	3	75.0	9
			5.0	5	62	0	0.0	7
			7.5	5	18	1	5.6	7
			10.0	5	69	8	11.6	7
			15.0	5	7	2	28.6	7
			20.0	5	13	8	61.5	7
			80.0	35, 40	2	2	100.0	8
			10.0-80.0					8
		Guinea Pig	2.2	15	10	4	40.0	9
			8.7	15	6	2	33.3	9
		Monkeys	20.0-80.0	10+	see text for details			8
		Rats	24.0		see text for details			3
$CBrClF_2$	H-1211	Dog	0.5	5	4	0	0.0	1
			1.0	5	7	1	14.3	1
			2.0	5	4	2	50.0	1
			4.0	5	2	2	100.0	1
		Rabbit	2.0	5	2	0	0.0	1
			4.0	5	3	1	33.3	1
$C_2Br_2F_4$	H-2402	Dog	1.8	15	4	1	25.0	9
		Guinea Pig	1.8	15	10	1	10.0	9

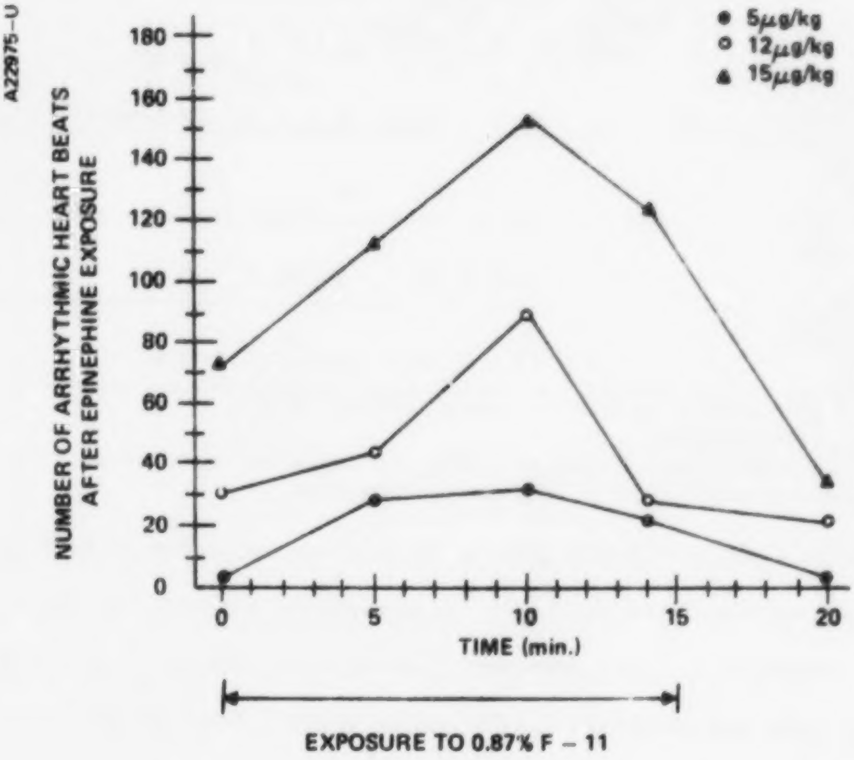

Figure 28: Number of Arrhythmic Heart beats in responses to different doses of epinephrine administered during exposure to 0.87% (V/V) F-11 (data from Wells, 1972).

Reinhardt and coworkers (1971) exposed dogs to varying concentrations of F-12 for periods ranging from .5 minute to 10 minutes (see Table LXIII).

Table LXIII: Cardiac responses of dogs exposed to F-12 for varying periods with challenge injections of epinephrine (Reinhardt et al., 1971)

Duration of Exposure	0.5 Min			5 Min		0.5 Hr	1 Hr
Concentration, % V/V	7.0*	7.0	13.5	2.5	5.0	(2.48-2.58)†	(2.48-2.50)†
No. of dog exposures	6	7	7	12	12	6	6
No. of marked responses	1	0	2(1)#	0	5(1)#	0	0
Percent marked responses	16.7	0.0	28.6	0.0	41.7	0.0	0.0

* Oxygen concentration reduced to approximately 8.0%.

† Analytic concentration.

# Numbers in parentheses indicate number of cases of ventricular fibrillation and cardiac arrest included in marked responses.

These results seem to indicate that a minimum concentration of F-12 in air is necessary to sensitize the heart to epinephrine and that increasing the period of exposure to lower concentrations will not result in arrhythmias. Similarly, Beck and coworkers (1973), using H-1211, indicate that as the duration of exposure is increased, the concentration necessary to cause arrhythmias decreases only to a point after which further exposure has no marked effect. Neither of these studies, however, are designed so that they would show a decreased response to epinephrine challenge with continued exposure as noted by Wills (1972). Even though this decreased effect may be of significance in determining the mechanism(s) involved in arrhythmias, most durations used in Table LXII are for five minutes, and as such, the comparative arrhythmagenic potentials of these compounds may be tentatively proposed. For the most part, the comparison is similar to that noted in standard inhalation studies: as fluorination increases within a homologous series, toxicity tends to decrease. Thus, for the fluoromethanes, the arrhythmagenic potency seems to be F-11 > F-12 = F-22. A similar pattern is seen in the perhalo-ethanes (F-113 > F-114 > F-115) and the bromochlorofluoromethanes (H-1211 > H-1301). However, as illustrated in Table LXIV, an attempt to compare the potencies among homologous series yields no definite pattern in terms of substitution.

Table LXIV. Percent of one and two carbon fluorocarbons causing arrhythmias in dogs on epinephrine challenge after exposure of five minutes (from Table LXII).

	Halo-substitution			% (V/V) Minimum Conc. Noted to Cause Arrhythmias	% V/V Maximum Conc. Causing No Arrhythmias
	F	Cl	Br		
F-11	1	3	0	0.35	0.32
F-113	3	3	0	0.40	0.27
H-1211	2	1	1	1.0	0.5
F-12	2	2	0	5.0	4.0
F-22	2	1	0	5.0	2.5
F-114	4	2	0	5.0	2.5
F-142b	2	1	0	5.0	2.5
H-1301	3	0	1	7.5	5.0
F-152a	2	0	0	15.0	5.0
F-115	5	0	0	15.0	-

Although such comparisons are of interest in determining relative potencies, the scope of Table LXIV is probably too narrow to be of any actual use other than demonstrating the lack of absolute correlation between halosubstitution and cardiac activity. For less readily absorbed compounds, exposure duration of longer than five minutes must be considered. In so doing, compounds such as F-116, H-1301 and H-1211 have sensitization potentials between F-12 and F-113. Indeed, current information of blood levels causing sensitization, as given in Table LXV, indicates that differences among the fluorocarbons may primarily reflect differences in absorption characteristics rather than any toxic mechanisms on the molecular level.

Table LXV: Blood levels, air concentrations, and exposure periods of various fluorocarbons causing cardiac sensitization.

Compound	% Exposure Conc.	Duration (Min.)	Number of Dogs Sensitized	Blood Concentrations (µg/ml) Arterial	Venous	Reference
F-11	0.1	10	0/12	10.9	6.6	Azar *et al.*, 1973
	0.5	10	1/12	28.6	19.7	Azar *et al.*, 1973
	0.63	5	0/4		10	Clark and Tinston, 1972a
	1.0	10	5/12	53.2	37.2	Azar *et al.*, 1973
			+		20-25	Jack, 1971
	1.5	5	2/4		20	Clark and Tinston, 1972a
F-12	0.1	10	N.D.	1.0	0.9	Azar *et al.*, 1973
	4.0	5	0/4		12	Clark and Tinston, 1972a
	5.0	10	5/12	35.3	22.6	Azar *et al.*, 1973
	8.0	5	2/4		35.0	Clark and Tinston, 1972a
	10.0	10	N.D.	66.3	39.4	Azar *et al.*, 1973
			+		[illegible]	Jack, 1971
F-114	5.0	5	0/4		13	Clark and Tinston, 1972a
	10.0	5	2/4		34	Clark and Tinston, 1972a
H-1211	8	1.0	2/4		21	Beck *et al.*, 1973
	5	2.0	1/4		23	Beck *et al.*, 1973
	2	5.0	2/4		24	Beck *et al.*, 1973
F-12/F-114	30/9	0.58	1/1*		[illegible]/1.8	Taylor *et al.*, 1971
		0.70	1/1*		6.3/2.3	Taylor *et al.*, 1971
		0.75	1/1*		6.5/2.2	Taylor *et al.*, 1971

*Monkeys
N.D. = not determined.

Although blood level data is currently available only on these four fluorocarbons, the remarkable similarities in lowest venous blood concentrations associated with cardiac sensitization in these various studies might lead one to suspect that these compounds act in a similar and perhaps nonspecific manner in causing arrhythmias. This type of speculation is at least circumstantially supported by the basic similarities in cardiac effects caused by these and other halo-substituted hydrocarbons.

Having briefly reviewed the basic dose-response results available on cardiac sensitization to injected epinephrine, certain details of some of these experiments should not be overlooked. As noted by Reinhardt and coworkers (1971), the results obtained with F-502 may indicate potentiation (see Table LXII). Fluorocarbon 502 - an azotropic mixture of F-22 and F-115 approximately 61:39 (V/V) respectively - causes multiple ventricular beats in five out of twelve dogs at a concentration of 10%--or 6.1% F-22, 3.9% F-115. Alone, however, F-22 at 5% causes multiple ventricular beats in only two out of twelve animals and F-115, at about four times its concentration in F-502, causes this response in only one of thirteen dogs. Although this data is quite limited, the possibility of potentiation is apparent.

Similarly, Reinhardt and coworkers (1971) observed a slight increase in response to 7.0% F-12 with hypoxia (see Table LXIII). Wills (1973) also notes that sensitization to injected epinephrine after exposure to 0.87% F-11 is increased by low oxygen tension and decreased by high oxygen tension. Although these observations are in themselves inconclusive, their possible relevance to cardiac sensitization to asphyxia induced arrhythmias cannot be ruled out (see Section XII, Part D-3).

The work of Call (1972) differs radically from the other investigations reported in this section and may be of only peripheral use in comparing results. Call's experiment tested the effects of a hypobaric atmosphere on the response of rats to F-1301. Epinephrine was administered at 10 μg/kg I.M. rather than I.V. The use of I.M. would be expected to produce much lower blood levels of epinephrine than I.V. injection. Hall and Norris (1958), for instance, have demonstrated that the lethal dose of epinephrine I.M. is about twenty times greater than the lethal dose I.V. in dogs exposed to fluothane. With these differences in mind, Call's (1972) observation of only one epinephrine injected rat out of twenty-seven developing premature atrial contractions after exposure to 24% H-1301 at 632 mm Hg. may reflect the low dose of epinephrine rather than any species difference in the response of rats to bromofluorocarbons.

Differences in species response to injected epinephrine have been noted by Beck and coworkers (1973) between dogs and rabbits, with dogs appearing to be twice as sensitive to H-1211 as rabbits.

Perhaps a more important species specific difference, at least in terms of assessing hazard to man, has been noted by Van Stee and Back (1969) between dogs and primates. Two anesthetized dogs exposed to 80% H-1301 and 20% O_2 for forty minutes and injected with 10 μg/kg epinephrine developed ventricular fibrillation followed by cardiac arrest. In other dogs, exposed to 20-80% H-1301 not showing arrhythmias, arrhythmias could be induced with 2-3 μg/kg epinephrine I.V. In these cases, a somewhat less than usual increase in blood pressure for the dosage of epinephrine was noted prior to onset of the cardiac response. In monkeys and baboons, however, an exposure to 80% H-1301 and 20% O_2 with 10 μg/kg epinephrine produced only brief transient periods of ventricular fibrillation and no cardiac arrests. Only one-half the normal increase in blood pressure was caused by a dose of 3-4 μg/kg in monkeys inhaling 80% H-1301/20% O_2. Further, a monkey did not show an increase in blood pressure with direct stimulation of the femoral nerve when exposed to 80% H-1301 which did cause a 20 mm Hg rise when breathing normal air. Subsequently, Van Stee and Back (1971b) demonstrated that the arrhythmic response to 30-80% H-1301 could be reversed by lowering blood pressure through venous bleeding and that an arrhythmic response to 10-20% H-1301 could be elicited by injecting epinephrine to raise the blood pressure. In the same study (Van Stee and Back, 1971b), blood pH was found to influence the blood level threshold at which arrhythmias occurred. Acidosis (blood pH of 7.10-7.30) increased the blood pressure threshold at which arrhythmias occurred on exposures of 10-20% H-1301 but had no effect in exposures of 30% or more as shown in Figure 29. A similar effect is noted by Flowers and Horan (1972) for unspecified fluorocarbon propellants at "high" concentrations. Eleven of the thirteen animals which survived exposure had blood pH levels below 7.35 and developed only sinus bradycardia. Conversely, eleven of the thirteen animals which died had pH levels between 7.35 and 7.47. All of this latter group exhibited asystole and ventricular fibrillation.

However, the arrhythmic response to injected epinephrine has not yet been completely defined and the role of fluorocarbons on the molecular level is little understood. The work of Wills (1972) illustrates the many different factors which need to be defined. In studies with F-11 and F-116,

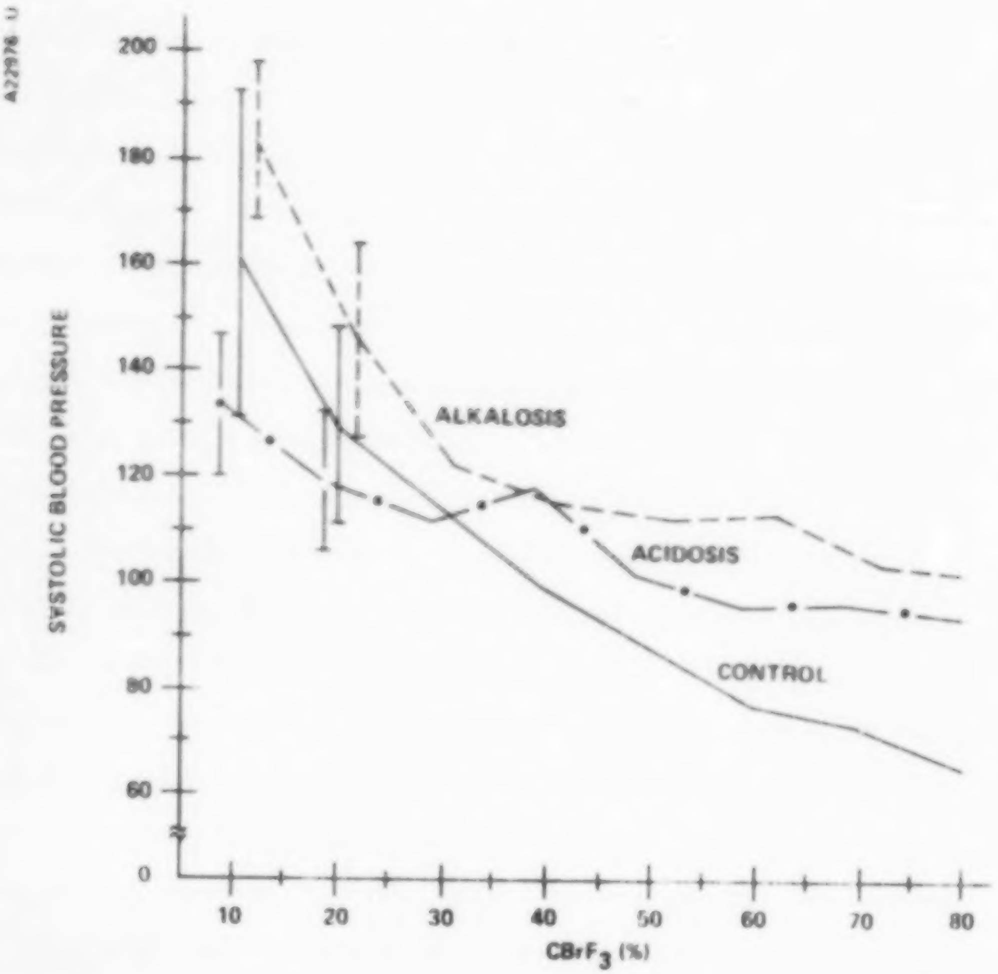

Figure 29: The minimal blood pressure necessary to trigger arrhythmias varied inversely with the concentration of $CBrF_3$ (Van Stee and Back, 1971).

Alkalosis elevated and acidosis lowered the blood pressure threshold during exposure to 10 and 20 percent $CBrF_3$ but was without significant effect at concentrations of $CBrF_3$ of 30 percent or greater. The vertical bars represent ± 1 standard deviation. Since no statistically significant differences existed above 20 percent $CBrF_3$ the standard deviations are not shown.

endogenous levels of norepinephrine was not influenced in the hearts of guinea pigs. Injections of another catecholamine, dopamine, did not increase sensitization. In terms of ion balance, blood plasma potassium level was not markedly affected by a fifteen-minute exposure to 0.4% F-11. Further, a 6 ml/kg I.V. injection of 3.3% $MgSO_4$ did not affect sensitization to injected epinephrine, which would further indicate that fluorocarbons do not alter the myocardial membrane permeability to potassium. While potassium may not be involved, the mycardial membrane permeability to calcium may be a factor. Preliminary experiments indicate that an infusion of $CaCl_2$ into cats (5 mg/kg/min.) produces cardiac sensitization to epinephrine similar to that of F-11. On the interneural level, both alpha- and beta-adrenergic receptors may be involved in that arrhythmias are prevented by either phenoxybenzamine or propanol, both of which block these receptors (Wills, 1972).

Young and Parker (1972) have used a vagal heart preparation from frogs (Rana pipiens) to measure the effects of fluorocarbons on cardiac arrhythmias. Similar to in vivo studies, F-12 was found to sensitize the heart to both direct sympathetic stimulation and exogenous epinephrine. F-12 (unspecified concentration) alone resulted in bradycardia and decreased contractility. With 10^{-7}g/ml epinephrine, partial then complete AV block was induced. Rhythmicity was restored by KCl but not Mg^{++}. Contractility was restored by the addition of glucose.

2. Cardiac Sensitization to Endogenous Epinephrine Induced Arrhythmias

In order to assess the relevance of experiments using injected epinephrine to conditions of stress, experiments have been designed to measure the effects of fluorocarbons on dogs presumably releasing high levels of endogenous epinephrine. Reinhardt and coworkers (1971) conducted "fright" experiments in which the release of endogenous epinephrine was induced by exposure to continuous loud noise while administering 80% fluorocarbon and 20% oxygen. The results of these experiments are given in Table LXVI.

Table LXVI: Cardiac Responses of dogs exposed to continuous loud noise and 80% fluorocarbon/20% oxygen for thirty seconds (Reinhardt _et_ _al_., 1971).

Compound	No. of Dog Exposures	No. of Mild Responses	No. of Marked Responses	Percent Responses		No. of Convul-sions	Percent Convul-sions
				Mild	Marked		
Fluorocarbon 11	12	9	2*	75.0	16.7	0	0.0
Fluorocarbon 114	12	1	1*	8.3	8.3	5	41.7
Fluorocarbon 12	12	2	0	16.7	0.0	9	75.0
Fluorocarbon 142b							
Compound & noise	12	4	5	33.3	41.7	9	75.0
Compound alone	12	3	1	25.0	8.3	5	41.7
Noise alone	6	1	0	16.7	0.0	0	0.0

* Bigeminal rhythm with areas suggestive of multiple ventricular beats.

A comparison of these results with those using exogenous epinephrine (see Table LXII under Reinhardt _et_ _al_., 1971) is difficult to interpret. In the exogenous experiments, the following order of potency, at concentrations varying from 0.1-5%, seems evident: F-11 > F-114 > F-142b = F-12. In these endogenous experiments, however, F-142b seems by far more potent eliciting cardiac sensitization even without the presumed induction of endogenous epinephrine by "fright". While F-12 produced no marked arrhythmias, it and F-114 did frequently induce marked tachycardia (300-500 beats/minute). In addition, the convulsions indicated in the above table are not identical.

Fluorocarbon-142b and F-12 produced convulsions characterized as "severe, generalized clonic, tonic seizures", while those elicited by F-114, however, were much less severe consisting of "spasticity of the extremities" (Reinhardt et al., 1971). Thus, on the basis of tachycardia, arrhythmias, and type of convulsion, all of these fluorocarbons may be distinguished from each other by the type of responses observed. However, to read too much into these results would be an error. The apparent shift in potency of F-142b may be insignificant in that the concentrations used are greatly increased (from 5% or less in exogenous experiments to 80%). The different responses noted may merely reflect differences in actual absorption of the various fluorocarbons because of different breathing patterns in the dogs or actual difference in absorptive characteristics of the compounds. Lastly, because of the method used to induce "fright"--i.e., "a loud noise provided by an amplified sound-effects tape recording having sounds of sirens, gongs, jet takeoffs, etc." (Reinhardt et al., 1971)--and the uncertain and possibly variable responses of dogs to fear, any conclusions drawn from the results must be tentative.

Procedurally, Mullin and coworkers (1972) overcome the difficulties associated with study of endogenous epinephrine by having the dogs run on a treadmill for twenty-one minutes at 300 feet per minute, referencing a study indicating that the circulating level of epinephrine increases by five-fold in dogs running at 300 feet per minute for fifteen minutes. The experimental protocol called for the first two minutes to serve as a control, the following sixteen minutes as an exposure period, and the last three minutes as a recovery period, with electrocardiograms being recorded continuously. The types of exposure and responses are given in Table LXVII.

Table LXVII: Cardiac responses of dogs exposed to various fluorocarbons while running (Mullin et al., 1972)

Test Compound	Concentration (% V/V)	Number of Dog Exposures		Number of Marked Responses	Percent Marked Responses	Comments
Air		6		0	0	
Fluorocarbon 12	5.0 (4.65 ± 0.49)^a					
	5.0^b	6		0	0	
	10.0^b	6	(3/6)*	1	16.7	Reaction questionable bigeminal rhythm or multiple ventricular beats (MVB's).
	10.0 (10.04 ± 0.44)	6		0	0	Ten percent levels not tolerated - exposures lasted from 1½ to 16 minutes.
Fluorocarbon 114	2.5 (2.53 ± 0.20)	6		0	0	
	5.0 (4.63 ± 0.23)	7	(2/3)	1	14.3	Five percent exposure repeated on four of the dogs, and the same dog had a [illegible] response. [illegible] response was MVB's [illegible] was bigeminal rhythm suggestive of MVB's.
	10.0 (9.44 ± 1.03)	7	(2/3)	1	14.3	Response was bigeminal suggestive of MVB's; reaction was at 1½ minutes after start of exposure; [illegible] 10% levels tolerated—exposures for compound lasted 1½ to 16 minutes.
Fluorocarbon 11	0.5 (0.46 ± 0.03)	6	(1/3)	0	0	All levels of this compound were well tolerated.
	0.75 (0.75 ± 0.12)	6	(1/3)	0	0	[illegible] exposure times lasted 1 to 16 minutes.
	1.0 (0.96 ± 0.11)	7	(3/4)	0	0	

^a Numbers in parentheses represent analytical concentrations ± standard deviation.

^b Nominal concentrations [illegible] concentrations given the dogs were probably [illegible]

*Fraction of prematurely terminated exposures as given by the original investigators in the text.

These results are somewhat difficult to interpret. All of the marked responses are those of a single and presumably "sensitive" dog and occurred between 1½ and 3 minutes of exposure when the amount of endogenous epinephrine induced by 3½ - 5 minutes of running is undetermined. Further, many of the exposures had to be terminated prematurely because the dogs became partially anesthetized. Thus, the value of the percentage figures given in Table LXVII is questionable. Nevertheless, Mullin and coworkers (1972), comparing their results with the screening experiments of Reinhardt and coworkers (1971), conclude that higher concentrations of these propellants are necessary to induce arrhythmias from endogenous epinephrine than from an injected dose of 0.008 mg/kg in dogs (see Table LXVIII).

Table LXVIII: Comparison of Results of Screening Experiments of Reinhardt *et al.*, 1971 and Treadmill Experiments of Mullin *et al.*, 1972 (Mullin *et al.*, 1972)

Test Compound	Concentration (% V/V)	Percent Marked Responses	
		Endogenous Epinephrine	Injected Epinephrine
Fluorocarbon 12	2.5	Not tested	0.0
	5.0	0	41.7
	Nom. 7.5	0	Not tested
	Nom. 10.0	16.7	Not tested
	10.0	0	Not tested
Fluorocarbon 114	2.5	0	8.3
	5.0	14.3	58.5
	10.0	14.3	Not tested
Fluorocarbon 11	0.1	Not tested	0.0
	0.5	0	8.3
	0.75	0	Not tested
	1.00	0	41.7

3. Cardiac Sensitization to Asphyxia Induced Arrhythmia

Perhaps the greatest controversy concerning the toxicity of the fluorocarbon gases has been stimulated by the work of Taylor and Harris (1970a), which may indicate that these compounds on inhalation are toxic to the hearts of mice. This toxicity is evidenced in fluorocarbon exposed mice by the rapid onset of sinus bradycardia and atrioventricular block induced by a degree of partial asphyxia which causes tachycardia in mice not previously exposed to the fluorocarbons. These investigators have reproduced their original findings in over 200 mice using F-11, F-12, and F-114 from a variety of sources (Harris, 1972b) and firmly assert the validity of both their technique and results (Harris, 1973). However, four other groups of investigators (Azar et al., 1971; Egle et al., 1972; Jack, 1971; McClure, 1972) using similar experimental techniques are unable to reproduce the results of Taylor and Harris in mice. Instead, they find that the effect caused by fluorocarbons does not vary significantly from those effects caused by nitrogen or asphyxia controls, i.e., bradycardia and AV block due to asphyxia and not related to fluorocarbon exposure. In review, Silverglade (1972) describes the conclusions of Taylor and Harris as having "no sound scientific basis" and characterizes their experimental approach as "poorly designed." Yet, Harris (1973) contends that the four other groups of investigators for the most part apply inappropriate degrees of asphyxia and their results, when valid, tend to confirm the original results of Taylor and Harris (1970a). Because the possible direct toxicity of these aerosol propellants is related to the interpretation of human deaths associated with aerosol abuse or unintentional overdose by asthmatics, the nature of the discrepancies between the results of Taylor and Harris and the findings of the subsequent investigators deserves careful attention.

Asphyxia can influence cardiac function in a variety of ways. A lowering of oxygen tension will increase the heart rate (tachycardia) but the heart, unable to acquire an oxygen debt, will eventually slow (bradycardia), become arrhythmic, and fail. Similarly, a small increase in carbon dioxide tension will stimulate vasoconstriction causing an increase in blood pressure and reflex bradycardia As carbon dioxide tension further increases, atrioventricular conduction is impeded, the heart slows and eventually stops. The crux of the Taylor and Harris (1970a and b) experiments is in producing a degree of asphyxia in the asphyxia-control mice that causes tachycardia and applying the same degree of asphyxia to mice previously exposed to fluorocarbons. Their basic approach is outlined below (Taylor and Harris, 1970a):

i) Anesthetize ICR adult mice with 0.5 ml of 0.3% pentobarbitol sodium (43-60 mg/kg).

ii) Insert snout of mouse into mouthpiece of commercial nebulizer (Medihaler-Iso® or Isuprel Mistometer®) for exposure to propellants or insert head into loosely fitted 5 ml. plastic bag containing 60% F-12 and 40% F-114.

iii) When using nebulizer, allow only single discharge (none in placebo group).

iv) Allow only three inspirations.

v) Asphyxiate "with a form-fitting plastic bag wrapped tightly around nostril and mouth, rostral to the ears."

vi) Continue asphyxia until 2:1 AV block [two atrial beats/ventricular contraction] or life-threatening sinoatrial (SA) bradycardia [subsequently defined as slowing of 200 or more beats per minute(Harris, 1972a)].

vii) Allow surviving animals to recover.

viii) Reapply asphyxia at 5, 10, 20, 40, 60, and 120 minutes after exposure.

Some of the results are given below in Table LXIX.

Table LXIX: Responses (Mean ± SE) of Mice to Asphyxia, Propellants, and Propellants plus Asphyxia (Taylor and Harris, 1970a).

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	No. of Mice	Changes in Heart Rate 25 Seconds After Asphyxia Begun (Beats/min)	No. of Mice Developing: 2:1 AV Block	No. of Mice Developing: Marked Sinus Bradycardia Without AV Block	Onset of Bradyarrhythmia After Asphyxia Begun (sec)
Group 1 Asphyxia and propellant					
Propellant	8	-66 ± 14.5	6	2	48 ± 4.9
Propellant and isoproterenol	4	-99 ± 36.7	[illegible]	2	36 ± [illegible]
Propellant and atropine	4	-114 ± 44.5	4	0	47 ± [illegible]
Mixture *	6	-83 ± 18.0	5	1	28 ± 6.9
Group 2 Asphyxia without propellant †					
None	4	+10 ± 6.5	0	0	...
After placebo	6	+47 ± 13.5	0	0	...
		Changes in Heart Rate 25 Seconds After Propellant Inhalation (Beats/min)			
Group 3 Propellant without asphyxia					
Propellant	4	-5 ± 9.8	0	0	...
Propellant and isoproterenol	4	+9 ± 19.2	[illegible]	0	...
Mixture *	4	-15 ± 5.0	0	0	...

* 60% dichlorodifluoromethane, 40% dichlorotetrafluoroethane mixture.
Asphyxia without propellant was applied for four minutes.

Further, of the 12 mice in Group 1 which survived the initial exposure to asphyxia, all died during subsequent asphyxia 10 to 160 minutes (average 50 minutes) without further exposure to propellants and without an increase in the time from asphyxia to arrhythmia. Similarly, mice from Group 3 developed 2:1 AV block in 24 ± 2.1 seconds when asphyxia was applied 15 minutes after fluorocarbon exposure.

Taylor and Harris (1970a) interpret their experimental results as cardiac sensitization to asphyxia-induced arrhythmias by the fluorocarbons. In a subsequent paper (Harris, 1972a), the duration of this effect is specified as 15-30 minutes. In that atropine, which supresses vagal inhibition of the heart, does not block the effect, Taylor and Harris (1970a) state that the bradyarrythmia may "more likely reflect a direct action on the SA node and AV conduction."

It is regrettable that in their study Taylor and Harris (1970a) omitted certain details from their presentation. Both Medihaler-Iso® and Isuprel® Mistometer are apparently used as sources of propellant. However, as T and coworkers (1971) indicated in a later paper, Medihaler-Iso® discharges 12.5 ml of gas while Isuprel® Mistometer discharges only 5.8 ml gas/activation. Further, Medihaler-Iso® contains F-11, F-12, and F-114, while Isuprel® Mistometer contains F-12 and F-114. Thus both the amount and types of propellants to which the mice were exposed varied. The significance of this variation cannot be evaluated from the data which Taylor and Harris present. Interpretation is further restricted by the lack of detailed time-response data. For instance, from the data presented in Table LXIX, atropine in combination with asphyxia and propellant seems to have a much greater depressant effect on heart rate at 25 seconds (-134 ± 44.5 beats/minute), than does propellant and asphyxia alone (-66 ± 14.5 beats/minute), but the atropine group requires a longer time to the onset of bradycardia (47 ± 5.7 seconds) than does the group exposed only to asphyxia and propellant (38 ± 4.9 seconds). Lastly, and probably most important, the investigators fail to describe in sufficient detail the technique that they used to apply asphyxia. Their description of a "form fitting plastic bag wrapped tightly around nostril and mouth" could quite reasonably be construed as total asphyxia. Subsequent publications (Harris, 1971, 1972a and b, 1973) have described partial asphyxia only in the effect that it causes - i.e., tachycardia in untreated mice - and not in the techniques used to induce it.

Using the Taylor and Harris (1970a) study as a model, Azar and coworkers (1971), Egle and coworkers (1972), and McClure (1972) have published relatively detailed reports on attempts to reproduce this effect under experimental conditions presumably approximating those of Taylor and Harris (1970a).

Azar and coworkers (1971) uniformly anesthetized the mice (60 mg/kg pentobarbital sodium, i.p.) and used four exposure groups: asphyxia alone, 100% F-12, 100% N_2, and a single discharge from Isuprel Mistometer® (5.8 ml mixture of F-12 and F-114, plus isoproterenol hydrochloride). Exposure lasted for five seconds and asphyxia was applied with "a close fitting vinyl mask." Besides these variations, the procedure seems to follow closely that of Taylor and Harris (1970a). The results are given below in Table LXX and Figure 30.

Table LXX: Responses (Mean ± SE) of Mice to Asphyxia (modified from Azar et al., 1971).

			No. of Mice Developing		
Condition	No. of Mice	Changes in Heart Rate 25 sec After Asphyxia Begun (Beats/min)	Heart Block	Marked Sinus Bradycardia Without Heart Block	Onset of Bradyarrhythmia After Asphyxia Begun (sec)
Asphyxia alone	12	-143 ± 48.2	5	7	64 ± 23.4
Nitrogen and asphyxia	12	-168 ± 43.6	9	3	18 ± 4.8
Isuprel Mistometer and asphyxia	12	-155 ± 41.6	10	2	30 ± 7.9
Dichlorodifluoromethane and asphyxia	12	-143 ± 33.9	9	3	23 ± 5.9

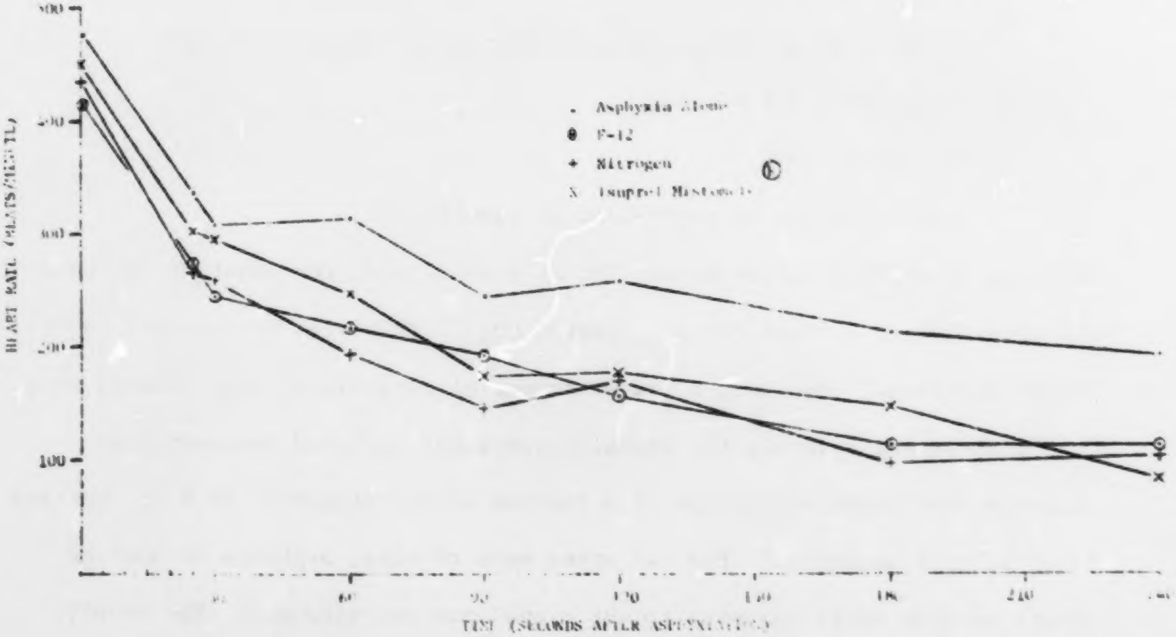

Figure 30: Heart rate response of mice exposed to compounds for five seconds followed by asphyxia (redrawn from Azar et al., 1971).

Similar to Taylor and Harris (1970a), atropine - 50 mg/kg i.p. - does not block bradycardia in nitrogen exposed mice indicating a direct effect on the heart rather than reflex inhibition. However, because there is no appreciable difference in nitrogen groups compared with the F-12 or Isuprel Mistometer® group, Azar and coworkers (1971) conclude that bradycardia and heart block is caused by hypoxia rather than the fluorocarbons.

Egle and coworkers (1972a, see also 1972b) report similar results with a greater variety of propellants and some significant modifications in experimental design. Along with an asphyxia control, the mice are exposed to the following compounds for five seconds:

> Propellant - one discharge of nebulizer, 70-77 mg [approx. 5.5-6.0 ml] 28% F-11, 72% F-12.
>
> Propellant and isoproterenol (100 μg and 70 μg/discharge).
>
> Propellant and albuterol
>
> Nitrogen, 100%
>
> [no variation in propellant is specified]

Asphyxia is applied in two ways. For most exposures, the snout of the mouse was covered with a "form fitting plastic bag." This will be referred to as "total asphyxia." However, a lesser degree of asphyxia is also induced when "the plastic bag covering the animal's snout was fastened somewhat less securely and permitted passage of a limited amount of air." This is referred to as "partial asphyxia." For two other sets of mice, asphyxia is applied thirty seconds after exposure to the propellant and nitrogen. The results are given in Table LXXI and Figures 31a and b.

Table LXXI: * Responses (Mean ± SE) of mice exposed to "total" and "partial" asphyxia (modified from Egle et al., 1972a).

Condition	No. of Mice	% Control Heart Rate at 24 seconds after Asphyxiation	Event AV Block	Event Bradycardia	Time to Onset of Event in Minutes
Total Asphyxia with immediate exposure					
Propellant (alone)	8	71 ± 7	1	7	0.66 ± 0.09
Propellant and isoproterenol (100 μg)	6	89 ± 10	3	3	0.67 ± 0.06
Propellant and isoproterenol (70 μg)	6	101 ± 3	3	3	0.73 ± 0.06
Propellant and albuterol	6	103 ± 10	0	6	0.93 ± 0.08
Asphyxia alone	11	94 ± 7	2	9	0.77 ± 0.08
Total Asphyxia with 30 second delay					
Propellant (alone)	4	88 ± 12	1	3	0.77 ± 0.06
Nitrogen	4	70 ± 7	0	4	0.78 ± 0.08
Partial asphyxia with immediate exposure					
Propellant (alone)	10	110 ± 6	4	6	1.80 ± 0.14
Nitrogen	5	113 ± 15	1	4	2.50 ± 0.29
Asphyxia (control)	13	104 ± 5	11	2	2.51 ± 0.20

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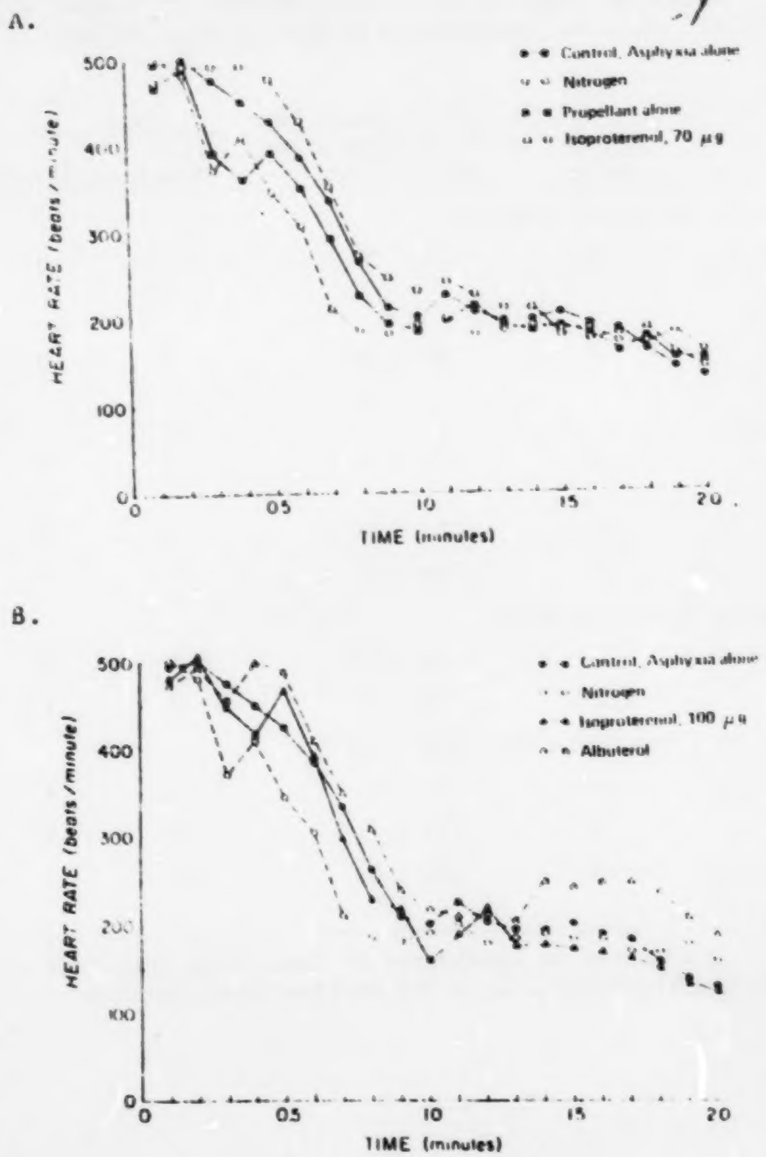
* In this table, 2:1 AV block is considered at least five instances of 2:1 AV Block per 0.1 minutes and bradycardia as a 50% decline from controls.



Figures 31a and b: Heart rates during total asphyxia of control (asphyxia alone) mice and animals exposed to nitrogen; as well as (a) propellant alone, and propellant with isoproterenol (70 μg): (b) propellant with isoproterenol (100 μg) and propellant with albuterol [from Egle et al., 1972b].

As with the previously discussed study (Azar et al., 1971), the authors conclude that their results do not support those of Taylor and Harris (1970a) and that the cardiac responses noted are caused by hypoxia (Egle et al., 1972).

McClure (1972) similarly exposed anesthetized mice (pentobarbital sodium, 65 mg/kg i.p.) to asphyxia, after three inhalations of propellant (approximately 12 ml; 25% F-11, 50% F-12, 25% F-114), and asphyxia after three inhalations of the propellant with 0.075 mg isoproterenol. Asphyxia was applied by "placing a small finger cot over the snout of the mouse." There are no other apparent differences of significance in the experimental approach from those outlined previously. The results, as presented by McClure (1972), are given in Table LXXII.

Table LXXII: Responses (Mean ± SD) of Mice to Asphyxia (McClure, 1972)

Time[a]	No propellant (negative control) n = 12 Heart rate (beats/min)		Propellant n = 10 Heart rate (beats/min)		Propellant + isoproterenol n = 6 Heart rate (beats/min)	
	X ± SD	% Δ	X ± SD	% Δ	X ± SD	% Δ
Control	439 ± 62	-	474 ± 85	-	484 ± 42	-
15 Sec	415 ± 74	-5	454 ± 86	-4	477 ± 60	-2
30 Sec	411 ± 35	-7	470 ± 88	-1	500 ± 40	+3
1 Min	435 ± 84	-1	453 ± 70	-4	510 ± 55	+5
2 Min	350 ± 52[c]	-20	425 ± 84	-10	514 ± 84	+6
4 Min	317 ± 74[d]	-28	394 ± 42[b]	-17	482 ± 62	-1
P-R interval[e]	3/12 (increase)		4/10 (increase)		3/6 (increase)	
QRS amplitude[e]	10/12 (decrease)		8/10 (decrease)		6/6 (decrease)	
Arrhythmias	9/12		7/10		3/6	
2:1 AV block	4/12		9/10		3/6	
Deaths	6/12		4/10		3/6	

a Time during asphyxia.
b Significantly different from control p <0.02.
c Significantly different from control p<0.01.
d Significantly different from control, p<0.001.
e Change from control.

As with the previous two studies (Azar et al., 1971 and Egle et al., 1972), McClure (1972) concludes that fluorocarbons do not significantly influence the cardiac response of mice to asphyxia. Jack (1971), in summarizing the work of Allen and Hansbury, Ltd. (1971), reports that in similar experiments the same conclusion is reached.

The information as presented in this series of studies is not only difficult to resolve but also awkward to compare: besides the eight different types of propellants or propellant with active agent combinations - with only two types being used by more than one investigator - many of the results are not expressed in the same way. Thus, to facilitate a comparison between these studies, data concerning the effect of propellant exposure and asphyxia on heart rate is presented in Table LXXIII as percent of original heart rate 25 seconds after asphyxia or after exposure to the propellant in cases where no asphyxia is applied. It should be emphasized that because of the various ways that the data is presented in the original papers, this comparison is, in some cases, only approximate (see notes to Table LXXIII). Similar data on the number of mice experiencing 2:1 AV block or bradycardia and the time to onset of these events after application of asphyxia is presented in Table LXXIV.

Table LXXIII: Percent change in the heart rates of mice at 25 seconds after exposure to various fluorocarbon propellants and nitrogen with and without asphyxia.

Prop 1a = 60% F-12; 40% F-114 inhaled from nebulizer, 1 activation
Prop 1b = 60% F-12; 40% F-114 inhaled from 5 ml plastic bag, 3 activations
Prop 2 = 50% F-12; 25% F-114, 25% F-11, inhalted from nebulizer, 1 activation
Prop 3 = 72% F-12; 28% F-11, inhaled from nebulizer, 1 activation

Conditions	Taylor and Harris, 1970a[1]	Azar *et al.*, 1971[2]	Egle *et al.*, 1972[3]	McClure, 1972[4]
Propellants and Asphyxia				
Prop. 1a or 2	-14 ± 2			-1 ± 18
Prop. 1b	-17 ± 4			
Prop. 3			-29 ± 7, +10 ± 6,[+] -12 ± 12[*]	
F-12 (100%)		-34 ± 8		
Prop. 1a or 2 and Isoproterenol	-21 ± 8	-34 ± 9		-1 ± 10
Prop. 3 and Isoproterenol 100 µg			-11 ± 10	
70 µg			+ 1 ± 3	
Prop. 1a or 2 and Atropine	-28 ± 9			
Prop. 3 and Albuterol			+ 3 ± 10	
Asphyxia (alone)	+ 6 ± 1	-30 ± 10	-6 ± 7, +4 ± 5[+]	-6 ± 6
Asphyxia with placebo	+ 9 ± 3			
N_2 (100%) and Asphyxia		-39 ± 10	-30 ± 7[*] +13 ± 15[+]	
No Asphyxia				
Prop. 1a or 2	-1 ± 2			-3 ± 7
Prop. 1b	-3 ± 1			
Prop. 1a or 2 and Isoproterenol	+2 ± 4			-1 ± 8

[1] Calculated from mean control heart rate of 482 for all 46 animals.
[2] Calculated by readings from Fig.30 (this paper) of initial heart rates.
[3] Reading at 24 seconds after asphyxia.
[4] Data from linear graph of Table LXXII (this paper). SD approximated, and Table 1 of McClure's paper.
[*] 30 second delay between end of exposure and asphyxia.
[+] Termed "partial asphyxia" by Egle *et al.*, 1974

Table LXXIV: Number of Mice Which Experienced and Time to Onset of 2:1 AV Block and Bradycardia.

	Taylor & Harris, 1970a			Azar et al., 1971			Egle et al., 1972			McClure, 1972		
Asphyxia with	Time to Onset (seconds)	No. of 2:1 AV Blocks	No. of Brady-cardia	Time to Onset (seconds)	No. of 2:1 AV Blocks	No. of Brady-cardia	Time to Onset (seconds)	No. of 2:1 AV Blocks	No. of Brady-cardia	Time to Onset (seconds)	No. of 2:1 AV Blocks	No. of Brady-cardia
Propellant 1a or 2	38 ± 4.9	6/8	2/8								9/10	7/10
Propellant 1b	28 ± 6.9	5/6	1/6									
Propellant 3							39 ± 5.4 46 ± 3.6* 108 ± 8.4+	1/8 I/4 4/10	7/8 3/4 6/10			
F-12 (100%)				23 ± 5.9	9/12	3/12						
Propellant 1a or 2 and Isoproterenol	36 ± 2.4	2/4	2/4	30 ± 7.9	10/12	2/12					3/6	3/6
Propellant 3 100 µg							40 ± 3.6	3/6	3/6			
and Isoproterenol 70 µg							44 ± 3.6	3/6	3/6			
Propellant 1a or 2 and Atropine	47 ± 5.7	4/4	0/4									
Propellant 3 and Albuterol							56 ± 4.8	0/6	6/6			
N_2 (100%)				18 ± 4.8	9/12	3/12	47 ± 4.8* 150 ±17.4+	0/4 1/5	4/4 4/5			
Asphyxia alone	> 240			64 ± 23	5/12	7/12	46 ± 4.8 150 ± 12+	2/11 11/13	9/11 2/13		4/12	9/12

* 30 second delay; + "partial asphyxia"; Propellant Key: same as Table LXXIII.

A number of factors might account for the wide variety of experimental results both within and among the various studies. Although there is little evidence in these studies to indicate that the different propellants used have markedly different effects, such a possibility cannot be ruled out. Further, potential effects of albuterol (Egle et al., 1972) and to a lesser extent atropine (Taylor and Harris, 1970a) may deserve more careful investigation.

Based on the conclusions drawn by Azar and coworkers (1971), Jack (1971), Egle and coworkers (1972) and McClure (1972), Taylor and Harris (1970a) may have been mislead by their failure to use a nitrogen control and what they observed as cardiac toxicity might merely be the effect of anoxia on the somewhat more hypoxic propellant exposed mice. This explanation is supported by the time-response data presented by both Azar and coworkers (1971) and Egle and coworkers (1972) [see Fig. 30 and 31a, respectively] indicating that exposure to either propellants or nitrogen results in a somewhat greater degree of asphyxia-induced bradycardia than does asphyxia alone. However, Taylor and Harris (1970a) indicate that rapid (24 ± 2.1 seconds) 2:1 AV block developes in mice allowed to recover for fifteen minutes after propellant exposure before asphyxiation and that this response does not develop without propellant exposure.

Harris (1973) proposes that the other investigators do not duplicate the results of Taylor and Harris (1970a) because they apply an incorrect degree of asphyxia. Based on the available time-response data on exposure to asphyxia alone, presented in Figure 32, this explanation seems plausible.

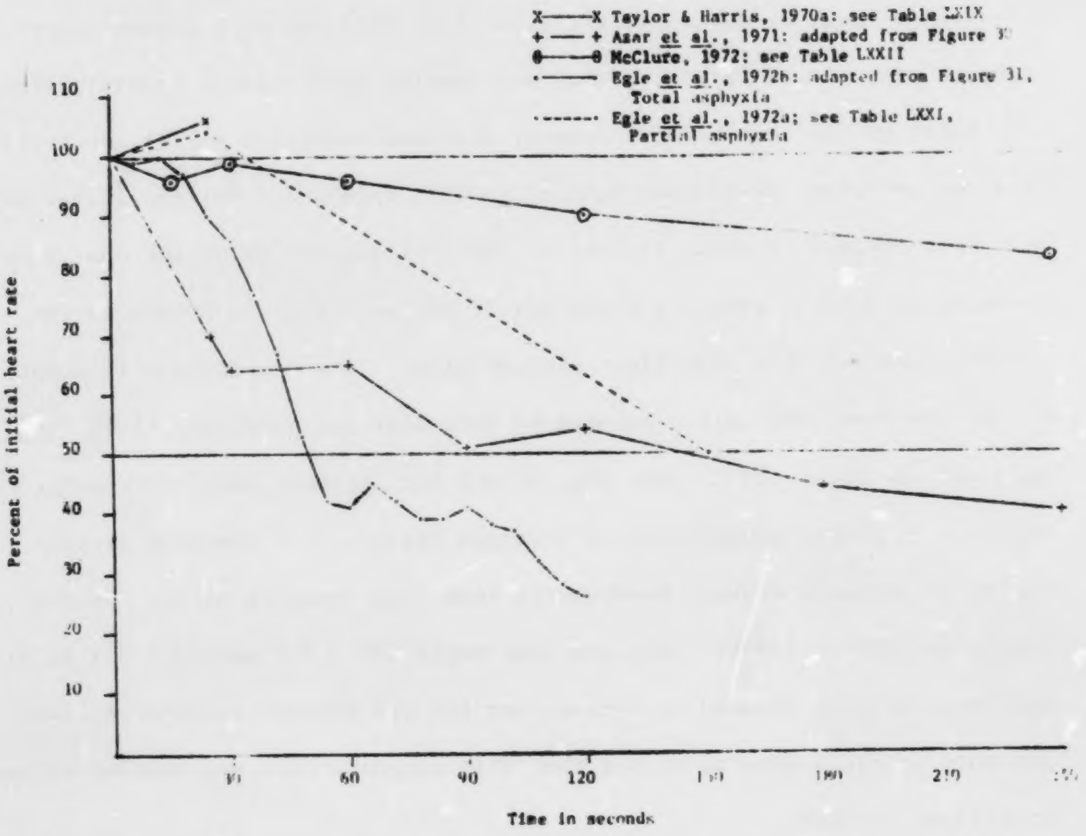


Figure 32: Percent Change in Heart Rate After Exposure to Asphyxia Based on Data from the Above Sources

Given this data, some of the criticisms by Harris (1973) do seem warranted. Azar and coworkers (1971) and Egle and coworkers (1972) - using total asphyxia - do seem to use a degree of asphyxia that might mask any possible demonstration of fluorocarbon cardiac toxicity. Harris (1973), however, is probably in error when he classifies the "partial asphyxia" (Egle *et al.*, 1972a) as closer to his earlier work (Taylor and Harris, 1970a) than that of McClure (1972). Although Egle and coworkers (1972) do not give detailed time-response data for partial asphyxia, the tachycardia at twenty-four seconds is probably quite transitory as indicated by the relatively rapid onset (151 seconds) of 50% bradycardia. Nevertheless, all of these investigators do use a degree of asphyxia that, when measured in terms of heart rate response, varies noticeably from that of Taylor and Harris (1970a).

The conclusion to be drawn from this rather detailed comparison of these various studies is inescapable in terms of technique but inconclusive as to the results. The technique used to apply asphyxia is in all probability, the critical step. These techniques are described as "a plastic bag wrapped tightly around the nostril and mouth" (Taylor and Harris, 1970a), "a close fitting vinyl mask" (Azar *et al.*, 1971), "a small finger cot over the snout" (McClure, 1972), "covering the snout with a form-fitting plastic bag" or the same "fastened somewhat less securely" (Egle *et al.*, 1972a). Such techniques and descriptions seem somewhat vague. This controversy has occupied a great deal of space in a variety of review articles and letters to the editor columns. It addresses an important aspect of fluorocarbon toxicity of concern to manufacturers, physicians, patients, and the public at large. Thus it seems peculiar that no published tests of this effect have been run in controlled atmospheres in which the amounts of oxygen, carbon dioxide, and nitrogen necessary to induce prolonged tachycardia could be monitored and the effects of various concentrations of different propellants measured.

Given the results that are available, no firm conclusion can be drawn. Harris (1973) seems to have effectively countered the results of Azar and coworkers (1971) and Egle and coworkers (1972) on the basis of inappropriate degrees of asphyxia. However, the attempt by Harris (1973) to use part of the data of Egle and coworkers (1972a) to support his results is rather feeble. Egle and coworkers (1972a) did notice a difference with "partial asphyxia" in the onset time of bradycardia (50% decrease) and 2:1 AV block between asphyxia alone exposures (150 ± 12 seconds) and asphyxia after propellant exposures (108 ± 8.4 seconds). However, given the limited time-response data (see Figure 32), it seems likely that the asphyxia alone group was also showing marked bradycardia at 108 seconds. Thus, while this difference may be significant statistically by $P<.02$ (Harris, 1973), its physiological significance may prove tenuous.

By far the most damaging evidence to the conclusions of Taylor and Harris (1970a) is the work of McClure (1972). McClure (1972) seems to maintain a degree of asphyxia only moderately greater than that of Taylor and Harris (1970a) with bradycardia never exceeding minus seventeen per cent during the first four minutes in the asphyxia alone group (see Figure 32). Thus, if the same degree of asphyxia is applied after exposure to a propellant, McClure (1972) should still be able to note a profound decrease in heart rate as might be expected by the conclusions of Taylor and Harris (1970a). No such observation is reported (see Table LXXII). That McClure (1972) did note an AV block in 4/12 of the mice exposed to asphyxia alone but a 9/10 incidence of AV block in the propellant plus asphyxia group may again be significant - P<.025 (Harris, 1973). However, considering that there is no marked difference in the number of mice showing arrhythmias or fatal exposures, and no indication of the time to onset of AV block, the actual significance of the 9/10 figure cannot be fully appreciated.

Assuming that the results of both Taylor and Harris (1970a) and McClure (1972) are valid indications of the cardiac toxicity of fluorocarbon propellants, the following characterization might be proposed: under conditions of mild asphyxia that would normally cause tachycardia, the propellants may cause rapid and pronounced bradycardia and AV block in mice but as the severity of asphyxia is increased, the toxic response is either inhibited or masked. This characterization, however, is merely speculative. Further experimental work, in which the various relevant parameters are closely monitored, would be necessary to define this effect.

4. Arrhythmias Not Associated with Asphyxia or Epinephrine

A variety of fluorocarbons have been found to affect cardiac function under conditions of adequate oxygenation or in the absence of elevated epinephrine levels.

Studies dealing with adequate oxygenation parallel closely those of asphyxia-induced arrhythmias as described above. Arrhythmias, in the absence of hypoxemia or hypercarbia, has been demonstrated both in dogs (Flowersand Horan, 1972b) and monkeys (Taylor et al., 1971).

Flowers and Horan (1972b) exposed dogs to a mixture (unspecified) of F-11 and F-12 by spraying this mixture on the inside of a plastic bag and fastening the bag "loosely over the head of the dog, allowing the active agent to be present in high concentration". In a group of six dogs, the bag was continuously oxygenated; in the remaining dogs, the only oxygen supply was by incidental mixing with room air. At the first indication of cardiac disturbance, the bag was removed. Although this technique does not allow an accurate estimation of the fluorocarbon dose, measurements were made of blood P_{o_2} and P_{co_2}. In the dogs receiving direct oxygenation, no significant changes were seen in these values. In dogs not receiving supplementary oxygen, P_{co_2} remained at control levels but there was a fall in P_{o_2} from a control level of about 75 mm Hg to post-exposure level of about 40 mm Hg. Although this fall is significant, it is not so marked as those "usually associated with profound or dangerous hypoxia" (Flowers and Horan, 1972).

In spite of sufficient oxygenation as demonstrated by blood gas measurements, the same types of arrhythmias were noted in both groups of dogs.

These arrhythmias included sinus bradycardia, AV dissociation or AV block, sinus arrest, and asystole. The details of the various responses are given in Table LXXV.

Table LXXV: Cardiac Responses of Dogs to a Mixture of F-11 and F-12 from Antiseptic or Hair Spray (Flower and Horan, 1972b).

Arrhythmias, Onset Time, and Mode of Death*

Experiment and Substance	Rhythm and Onset Time	Death
1 Antiseptic Spray	SB → SA + VE → VT → 8 min	VF
2 Antiseptic spray	SB → VE + AVR → VT → 10 min	K
3 Antiseptic spray	SB → 1 min	Acc
4 Antiseptic spray	SB → VPBs → 1 min	K
5 Antiseptic spray	SB → VE + RCA → 5 min	VF
6 Antiseptic spray	SB + 1° AVB → JE + RCA → VE + RCA → 4 min	A
7 Antiseptic spray	SB + 1°AVB → SA + JE → VE → 4 min	A
8 Hair spray	SB → VT → 1 min	K
9 Hair spray	SB → VPB → 20 min	K
10# Antiseptic spray	SB → 3 min	K
11 Antiseptic spray	SB → AJR → SB → 45 sec → JE → SA + VE →	A
12 Antiseptic spray	SB + 1° AVB → SA + VE → 4 min 55 sec	A
13 Antiseptic spray	SB → 10 min	K
14 Antiseptic spray	SB → 3° AVB + VE → SB + 2° AVB → 8 min → SB + 1°AVB → JE → JS + VE → → VT →	A
15 Antiseptic spray	SB → AJR → JS + VE → 45 min	A

*SB signifies sinus bradycardia; SA, sinus arrest; JE, junctional escape; JS, junctional slowing; VE, ventricular escape; AJR or AVR, accelerated junctional or ventricular rhythm; RCA, retrograde conduction to the atria; VPB, ventricular premature beats; VT, ventricular tachycardia; K, killed; Acc, accidental deaths; VF, venticular fibrillation; A, asystole.

#Supplemental oxygen supplied in dogs #10-15.

In several species of monkeys, a fluorocarbon mixture - 30 ± 2.0% F-12 and 9 ± 0.5% F-114 in either compressed air or 100% oxygen - is reported to induce ventricular arrhythmias in the absence of hypoxemia or hypercarbia (Taylor et al., 1971). In this study, fourteen conscious or anesthetized monkeys are exposed to compressed air (3), asphyxia (4), or 100% nitrogen (7) for three minutes, allowed to breathe room air for fifteen or thirty minutes, then exposed to the fluorocarbon-oxygen mixture (all 14) until the appearance of the first ventricular extrasystole. After a thirty minutes recovery period, three of the animals are re-exposed to the fluorocarbon mixture and the remaining eleven are given a two-minute I.V. infusion of 0.07 mg/kg propanolol hydrochloride [to block beta adrenergic receptors] and, after fifteen minutes, are re-exposed to the fluorocarbon mixture for two minutes or until arrhythmias or convulsions appear. Arterial Po_2, Pco_2, pH, blood pressure, and fluorocarbon concentration are monitored in various animals.

As indicated in Table LXXVI, the fluorocarbon mixture does not significantly alter arterial Po_2, Pco_2, or pH, whereas the 100% nitrogen does cause marked hypoxemia as compared to control.

Table LXXVI: Effects of (Mean ± SE) of Nitrogen and Fluorocarbon Exposure on Po_2, Pco_2, and pH of Arterial Blood in Seven Monkeys (modified from Taylor et al., 1971)

Conditions	Po_2		Pco_2		pH	
Control	106	6.2	26	2.7	7.41	0.01
Nitrogen	30	3.2*	26	2.3	7.39	0.03
Fluorocarbon	121	5.5	23	1.5	7.39	0.03

*Significantly different from control and fluorocarbon values (P <0.001).

Exposure to compressed air, asphyxia, or 100% nitrogen for three minutes failed to produce any arrhythmias, except in one nitrogen exposed animal with an arterial blood Po_2 of 16 mm Hg which experienced ventricular premature beats at 105 sec.

Exposure to the fluorocarbon mixture, however, produced cardiac irregularities in all monkeys, the details of which are given in Table LXXVII.

Table LXXVII: Cardiac Responses of Monkeys to Fluorocarbon Inhalation (data from Taylor *et al*., 1971)

Event	Number/Animals Experiencing Event	Rate (per minute) Measured in 3 sec. intervals Mean ± SE	Range	Time to Onset (seconds) Mean ± SE	Range	Duration (Seconds)
Extrasystoles						
Initial	14/14	40 ± 7	8-90	39 ± 4.2[+]	20-72	30-180*
Maximum	11/14	90 ± 11	25-120		10-30#	
Bigeminy	3/14					
Ventricular Tachycarida	4/14					

*Recovery time breathing room air and excluding those monkeys experiencing bigeminy of ventricular tachycardia.
+Time to onset after exposure to propellant mixture.
#Time to onset after appearance of initial extrasystoles.

A similar pattern of increase in the rate of extrasystoles despite the discontinuance of fluorocarbon gas after the initial appearance of premature ventricular beats is seen in Table LXXVIII for three monkeys exposed twice to the propellant mixture.

Table LXXVIII: Individual Cardiac Responses of Three Monkeys Exposed Twice to Fluorocarbon Inhalation (data from Taylor et al., 1971).

Monkey # :	First Exposure #1	First Exposure #2	First Exposure #3	Second Exposure #1	Second Exposure #2	Second Exposure #3
Time to Ventricular Extrasystoles (sec.)	30	42	35	25	36	20
Initial Frequency (per minute)	18	40	60	20	30	60
Maximum Frequency (per minute)	120	80	110	40	110	120

The arterial blood levels of the fluorocarbons at the onset of ventricular premature beats are given in Table LXXIX.

Table LXXIX. Arterial Blood Levels of F-12 and F-114 at Time of Onset of Ventricular Premature Beats in Monkeys

Time of Onset (seconds)	Arterial Blood Concentrations (mg/100 ml) F-12	F-114	Total
35	5.5	1.8	7.3
42	6.3	2.3	8.6
45	6.5	2.2	8.7

Fluorocarbon inhalation caused a decrease in blood pressure just prior to ventricular arrhythmias. The type, time to onset, and frequencies of the arrhythmic responses are apparently not influenced by anesthesia, but extrasystoles is blocked by propanolol.

These results may be interpreted in two general ways (Taylor et al., 1971). First, the fluorocarbon gases at the concentration observed may be exerting a direct stimulating effect on the beta adrenergic receptors or some direct toxic effect on the myocardium. Secondly, they may have sensitized the ventricular myocardium to endogenous catecholamines and/or stimulated the release of such catchecolamines. This latter interpretation is consistent with the blocking of arrhythmias by propanolol.

The cardiovascular effects of the brominated fluorocarbons, especially H-1301 and H-1211, have been extensively studied because of their use as fire extinguishing agents. Although some of these studies have been concerned with sensitization to epinephrine-induced arrhythmias as discussed in a previous section, much of the work has been conducted without injected epinephrine or attempts to induce endogenous epinephrine. Van Stee and Back (1969) have described the effects of H-1301 at concentrations of 20-80% in dogs as tabulated below.

Table LXXX: Cardiac Responses of Dogs to Varying Concentrations of H-1301 in Oxygen (from Van Stee and Back, 1969).

Concentration	Response	Time to Onset After Start of Exposure
20-30%	Tachycardia (10-15%) in some animals	few seconds
	Arrhythmias T-wave depression unifocal and multifocal ventricular arrhythmias bi- and trigeminy	first minute of exposure (lasted until 2-4 minutes post-exposure.)
40%<	Tachycardia as above in all animals	few seconds
50%<	Blood pressure full of 20-60 mm Hg.	
	Irregular changes in heart rate proportional to cardiac output.	
	Decrease in pulse pressure to 0-30 mm Hg. from a normal of 45-50 mm Hg.	25-30 min.
	Lowering of peripheral vascular resistance.	
80%	More rapid decrease in pulse pressure	

All of the above-noted effects were reversible in about twice the time to onset

Monkeys exhibited the same type of arrhythmias as described in dogs.

Halon-1301 has also been evaluated under both hypo- and hyperbaric conditions. Rats were exposed under hypobaric conditions (632 mm Hg and 380 mm Hg) to 8, 16 and 24% H-1301 for five minutes (Call, 1972). The arrhythmias noted consisted of premature atrial contractions occurring after one minute of exposure. These occurred in only two out of twenty-seven rats, one at 24% H-1301 and 632 mm Hg and the other at 16% H-1301 and 380 mm Hg. However, as indicated by Call (1972), these results cannot be readily compared to the above work of Van Stee and Back (1969) because of probable species specific differences in response. Paulet (1962) has noted such variations in response to H-1301 in mice, rats, rabbits, and guinea pigs.

Cardiac response of cats to H-1301 under hyperbaric conditions have been studied by Greenbaum and associates (1972). Exposure of 5% H-1301 for 2 min. and 5 min. were given to cats pressurized at 73 psig (165 ft. sea level). Under these conditions, the partial pressures in inspired air were 228 mm Hg for H-1301, 866 mm Hg for O_2, and 3466 mm Hg for N_2. This is equivalent to 30% H-1301 at standard atmospheric pressure.

Table LXXXI: Cardiac Responses in Normal Cats and in Cats before, during and after H-1301 exposure at 165 ft. sea water (Greenbaum et al., 1972).

Group	Rate (mean with range)	PR interval (mean with range) (sec)	QRS duration (mean with range) (sec)
Normal	145(105-194)	0.08 (0.065-0.09)	0.037 (0.035-0.040)
Control	212(178-272)	0.08 (0.06-0.12)	0.050 (0.04-0.06)
2 min on Fe 1301	212(160-272)	0.08 (0.07-0.12)	0.056 (0.04-0.07)
5 min on Fe 1301	212(160-270)	0.08 (0.06-0.12)	0.060 (0.04-0.08)
1 min on air	212(155-288)	0.09 (0.07-0.12)	0.059 (0.04-0.08)

Three of the twelve animals showed abberent ventricular conduction associated with frequent nodal beats. This response is reflected in the slight increase in QRS duration in the average figure given for the 12 cats. In seven cats, responses ranged from infrequent premature atrial contraction to frequent nodal beats. Two cats did not show any abnormal cardiac activity. The blood pressures in 10 of 12 cats fell from a control mean of 160/115 to an exposure mean of 148/96. The range was a 10-50 mm Hg drop in blood pressure, which is quite similar to the hypotension noted by Van Stee and Back (1969) at comparable concentrations in dogs at standard pressure.

Halon-1211 shows a response sequence similar to H-1301 but a lower concentrations. Table LXXXII (Beck et al., 1973) summarizes the cardiac responses of dogs to H-1211 and should be compared to the data on -1301 in Table LXXX.

Table LXXXII: Cardiac Responses of Dogs to H-1211 (Beck et al., 1973)

Concentration	Duration	Response
1%	5 min.	no effect
2%	5 min.	tachycardia (20%), slight T-wave depression
5%	30 min.	tachycardia in all dogs; severe convulsion in 1 of 6 dogs followed by several ventricular ectopic beats, ventricular fibrillation and death
7%	15-30 min.	bursts of marked tachycardia (up to 350%) associated with convulsions

As with H-1301 exposed dogs, the tachycardia ceased in 1-2 minutes after exposure was discontinued. Further similarities of H-1211 to H-1301 can be noted in the cardiovascular response. At concentrations of 1% H-1211, a slight decrease in systolic blood pressure was noted. At 5% H-1211, a 10% decrease in blood pressure, slight T-wave depression, and occasional pulsus alternans were noted. At 20-30% H-1211, pulsus alternans became more frequent at ten minutes of exposure and were characterized by alternate strong and weak ventricular contractions. As with the other effects, these were reversible on return to normal air (Beck et al., 1973). Van Stee and Back (1972b) also report a fall in systolic blood pressure in dogs after exposure to 15% H-1211 for five minutes.

5. Cardiac Responses Related to Arrhythmias

In an attempt to better understand the arrhythmogenic activity of the fluorocarbons, various experiments have been conducted in attempts to define the cardiopulmonary, hypotensive and negative intropic effects of these compounds.

Aviado (1971) has measured the effects of F-11, F-12, and F-114 in dogs on pulmonary resistance and compliance, bronchial smooth muscle, pulmonary blood vessels and the heart in an attempt to determine if the cardiopulmonary effects of these propellants could be related to sensory receptor initiation in the respiratory tract. Exposure of only the upper respiratory tract (nose, pharynx, and larynx) to 200 ml of 50% F-11 resulted in apnea, bradycardia (-55%), and an initial decrease followed by an increase in aortic blood pressure with no significant changes in pulmonary resistance or compliance. Less severe bradycardia (not specified) was induced by F-114 but F-12 did not affect either cardiovascular responses. Exposure to the lower respiratory tract of F-11, F-12, F-114 at doses of 5, 10, 15, and 20 puffs (amount released/activation not specified) from an aerosol unit resulted in changes of pulmonary resistance and heart rate as indicated in Figure 33.

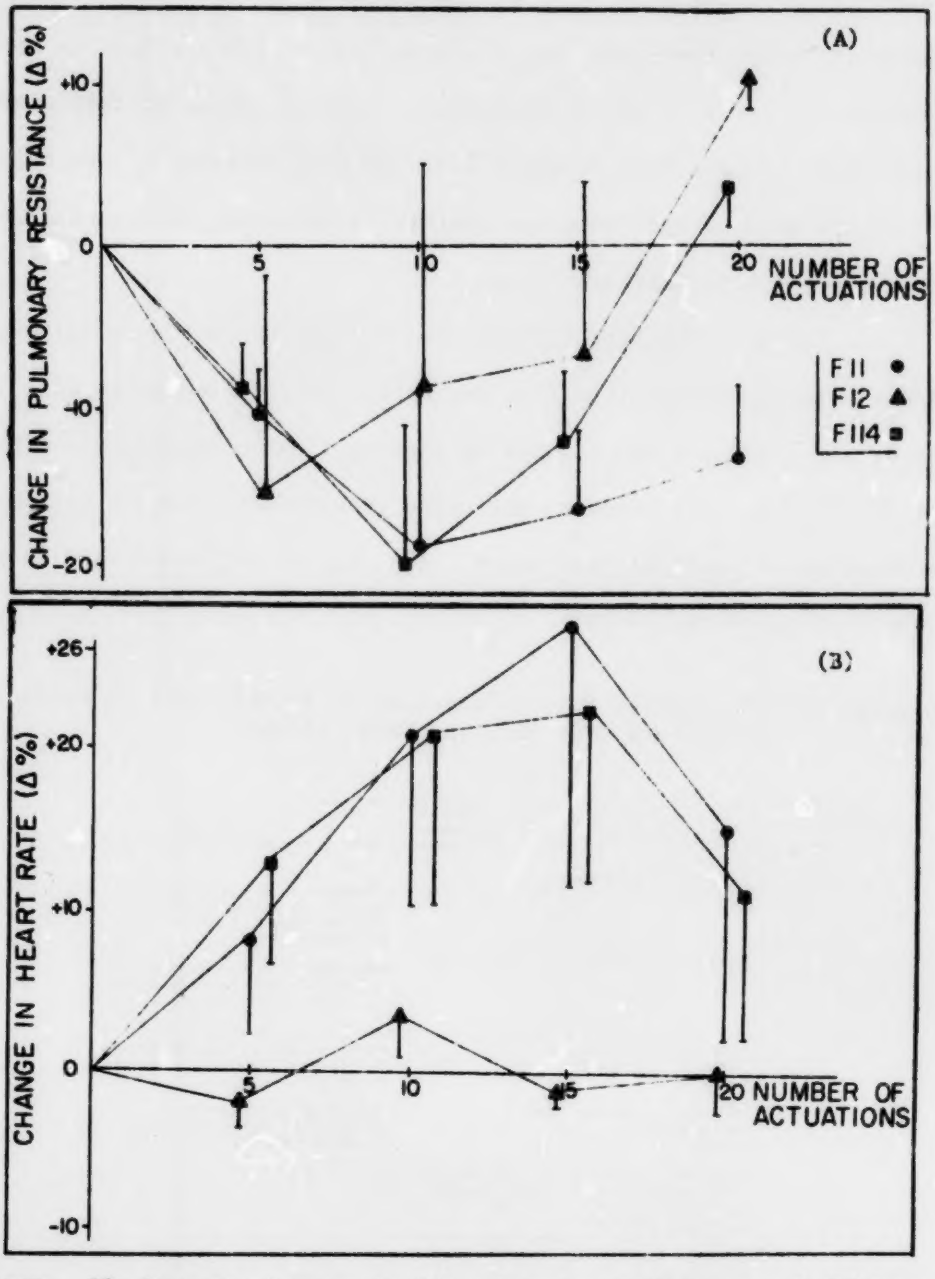


Figure 33: Percent changes in (A) pulmonary resistance and (B) heart rate following exposure of various propellants to the lower respiratory tract in dogs (Aviado, 1971).

As in exposure to the upper respiratory tract, F-12 did not alter heart rate and F-11 resulted in a slightly greater response than did F-114 but in this case causing tachycardia rather than bradycardia. The decrease noted in pulmonary resistance for F-11 was accompanied by a simultaneous increase in pulmonary compliance (maximum of 27% at 15 puffs) and a fall in aortic blood pressure (maximum of -8% at 15 puffs). Thoracic sympathectomy prevented tachycardia caused by F-11 and F-114. In that blocking of the beta adrenergic receptors with sotalol does not inhibit tachycardia, tachycardia is attributed to the sympathetic afferent fibers.

Van Stee and Back (1972a) have studied the mechanism by which H-1301 lowers blood pressure (Van Stee and Back, 1969; Greenbaum _et al_., 1972). Using pairs of male beagle dogs in cross-perfusion experiments with exposure of 70% H-1301, they measured perfusion pressure at constant perfusion flow as a function of vascular resistance. The results are summarized in Table LXXXIII (Van Stee and Back, 1972a).

Table LXXXIII: Responses of Dogs to Exposure of H-1301 (70%) in Cross-circulation Experiments (Van Stee and Back, 1972a).

Pharmacologic action on vascular smooth muscle	Direct response, donor dog exposed	Indirect (neurogenic) response, recipient dog exposed
Active vasodilation		
Activation of cholinergic receptors	No direct effect	Pretreatment of HL[a] vascular bed of recipient with atropine did not alter HL response to exposure of recipient to $CBrF_3$
Activation of β-adrenergic receptors	No direct effect	Pretreatment of HL vascular bed with propranolol did not alter HL response to exposure of recipient to $CBrF_3$
Passive vasodilation		
Inhibition of the activation of α-adrenergic receptors	No direct effect	Pretreatment of HL vascular bed with phenoxybenzamine greatly attenuated HL response to exposure of recipient to $CBrF_3$
Inhibition of sympathetic postganglionic activity	NA[b]	Pretreatment of recipient with hexamethonium abolished HL response to exposure to recipient to $CBrF_3$
Increased local concentration of tissue metabolites or other vasodilator substances	No effect on HL during exposure of donor	NA

[a] Perfused recipient hind limb.

[b] Not applicable.

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To measure the possible effects of ganglionic blockade, nictitating membrane tension was measured during electrical stimulation of the right vagosympathetic trunk in anesthetized dogs before, during and after exposure to 80% H-1301. A 40% decrease was noted in membrane tension during exposure, with a recovery period of 30 minutes post exposure. Further, vagal inhibition of the heart was significantly decreased.

These results seem to indicate that while direct alpha-adrenergic blockage may not be involved in decreased vascular resistance, ganglionic blockage may be an important factor (Van Stee and Back, 1972a).

In a similar cross-circulation experiment (Van Stee and Back, 1972b), H-1211 at 15% has also been shown to decrease peripheral vascular resistance in dogs. As with H-1301, this decrease was not associated with the peripheral adrenergic receptors. Lastly, neither H-1301 nor H-1211 have a direct effect on the peripheral vascular smooth muscle (Van Stee and Back, 1972 a and b).

Exposing anesthetized dogs to 70% H-1301, Van Stee and Back (1971a) noted a rise in left ventricular end diastolic pressure as an indication of reduced myocardial contractility. This has been subsequently shown to be a common characteristic of a variety of fluorocarbons.

Pursuing their initial observation, Van Stee and Back (1972b) demonstrated the negative inotropic effect of H-1301 in beagle dogs by measuring the maximum rate of ventricular pressure change divided by total pressure developed [peak dP/dt ÷ P] in exposure to 50% and 75% H-1301 for five minutes. As indicated in Figure 35, a definite dose-related reduction in myocardial contractility can be noted.

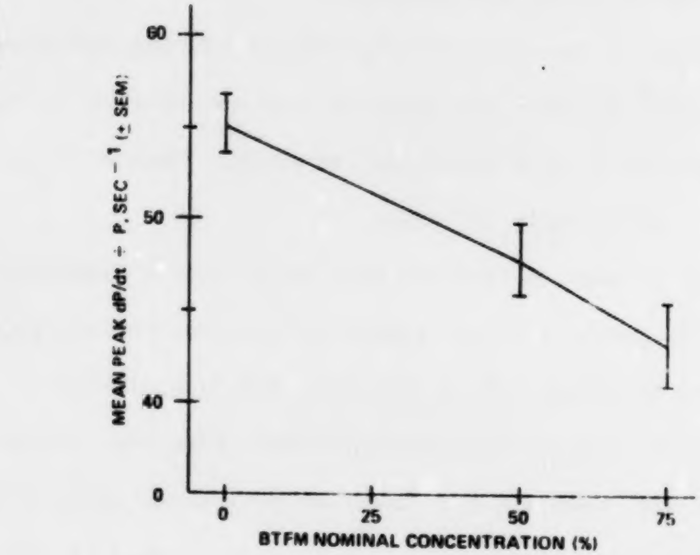

Figure 34: Decreased Myocardial Contractility in Dogs after Exposure to 50% and 75% H-1301 for Five Minutes (Van Stee and Back, 1972b)

Similar to arrhythmagenic potencies, H-1211 has been shown to reduce myocardial contractility at significantly lower concentrations. Beck and associates (1973), using a force displacement transducer, measured isometric contractions at the apex of the heart in open-chest spinal rats in exposures of 5%, 10% and 20%. The results are given in Figure 35.

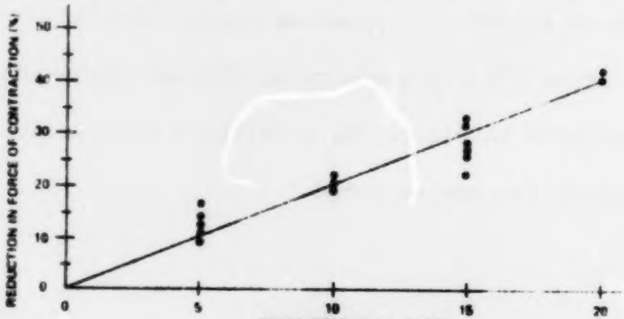

Figure 35: Changes in Isometric Contraction in Rats During Exposure to H-1211 (Beck *et al*., 1973)

The validity of continuing the regression line on the above graph is most questionable in that Beck and associates (1973) specifically mention that concentrations below 5% of E-1211 rarely produced any forced reduction. Azar (1972) has made a similar criticism of the data presented in Figure 34.

Fluorocarbon -12 has also been shown to reduce myocardial contractility over concentrations of 2-25% in close-chested cats (Taylor and Harris, 1972b). At 25% F-12 in inspired air, F-12 blood levels in cats reached (mean ± SE) 9 ± 0.4 mg/100 ml. This concentration increased end diastolic pressure by 1.6 ± 0.4 mm Hg and lowered arterial pressure from 133/93 to 101/65 mm Hg. At a left ventricular pressure of 60 mm Hg, the instantaneous rate of ventricular pressure developed dropped from 3369 to 1972 mm Hg/sec. The instantaneous velocity of contractile element shortening (dP/dt ÷ 32P) was decreased from 3.5 to 1.9 muscle lengths/sec.

Fluorocarbon -12 has also been shown to reduce the rate and the intensity of force development in rat mycardial tissue *in vitro*. The effect is dose-related and occurs in the presence or absence of adequate oxygenation. This has been demonstrated by Kilen and Harris (1972) using muscle bath preparations of rat left ventricular papillary muscles and exposing the baths to a variety of gas mixtures. The composition of these gas mixtures and their effect on Po_2 is given in Table LXXXIV. No significant effect is noted on either pH (mean, 7.53; range 7.46 - 7.67) or Pco_2 (Mean, 10; range 9 - 12).

Table LXXXIV: Conditions of Exposure of Rat Left Ventricular Papillary Muscles in Muscle Bath and the Effect on Po_2 (Kilen & Harris, 1972)

		%				ml/min.	min. Hg+
Condition	Code	O_2	CO_2	N_2	F-12	Flow Rate	Po_2
Control	O_2-CO_2	99%	1%	-	-	54.8	613 ± 7
Hypoxia	N_2-CO_2	-	1%	99%	-	68.8	36 ± 3
Nitrogen	N_2-O_2-CO_2	99% -	1% -	- 100%	- -	54.8 68.8	464 ± 18
Freon	CCl_2F_2-O_2-CO_2	99% -	1% -	- -	- 100%	54.8 42.8	493 ± 22
Hypoxia & Freon*		-	1%	99%	- 100%	68.8	32 ± 3

+ after 15 minutes

* Hypoxia for 30 min. with F-12 added in last 15 minutes reduced Po_2 to 26 ± 1 min Hg.

Time-response data for these exposures is given in Figure 36 and indicate that F-12 with adequate oxygenation decreases myocardial contractility more rapidly than does hypoxia although the amount of decrease is similar for both conditions at fifteen minutes.

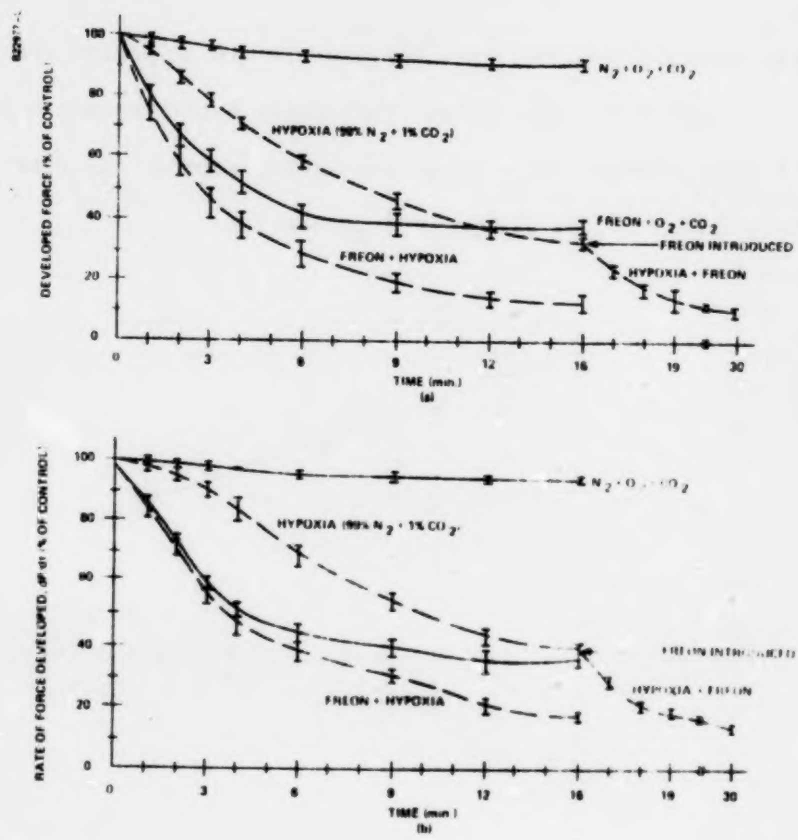

Figure 36: Effect of Exposures to Various Gases *in vitro* Mycardial Contractility (Kilen and Harris, 1972)

The effect of Freon plus hypoxia is engaging especially in view of the time-response data given in Figure 36. F-12 and hypoxia alone have similar effects at fifteen minutes although mechanisms, in view of the differences in oxygen tension and rapidity of depression, are probably different. The effects of F-12 and hypoxia together seem very much the same whether F-12 is administered directly with hypoxia from a well oxygenated state or after fifteen minutes of hypoxia alone. Although no time-response data is available for F-12 or hypoxia alone for thirty minutes, it might be concluded that the mechanisms of myocardial depression by F-12 and hypoxia are not only different but also quite independent of each other. The linear dose-response relationship of F-12 concentration to in vitro myocardial contractility is illustrated in Figure 37 for groups of 4-10 muscles.

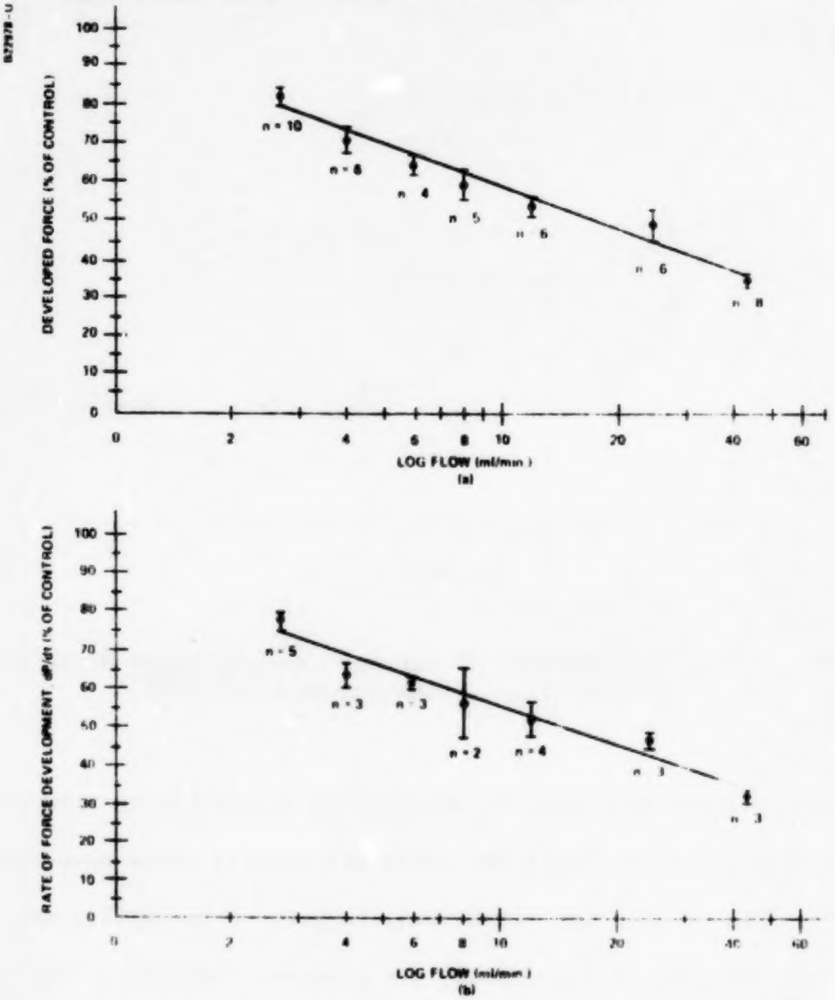

Figure 37: Dose-response curves for the effects of dichlorodifluoromethane gas (F-12) on isometric developed force in 15 isolated rat papillary muscles (A) and on maximal rate of isometric force development, dP/dt, in six of these muscles (B). Each point is the mean ± SE of four to ten muscles in A and two to five muscles in B. The n value next to each point is the number of muscles studied at that flow. The bath concentration of F-12 at 2.7 ml/min is 1.06 ± 11 mg/100 ml and at 42.8 ml/min is 11.35 ± 0.52 mg/100 ml (Kilen and Harris, 1972).

E. Sensitization - Repeated Doses

Hypersusceptibility on repeated dosing has not been clearly demonstrated in any of the fluorocarbon propellants, solvents, or fire extinguishing agents. In fact, Yant and coworkers (1932) note that dogs seem to develop a definite tolerance to repeated exposures to 14.16% F-114. The animals were exposed for eight hours per day for 21 days. After three days, dogs no longer convulsed, tremors were less severe, and they showed a less pronounced loss of equilibrium and increased alertness during exposure. After 18 to 20 days, the dogs showed no adverse effects to the exposure after the initial 30 seconds.

Fluorocarbon-112 did not produce sensitization when applied to the skin of guinea pigs (Clayton et al., 1964).

Repeated exposures to F-1211 did not result in increased sensitization to epinephrine induced arrhythmias (Beck et al., 1973).

F. Teratogenicity

There is no information indicating that the fluorocarbons under review are teratogenic. In long-term feeding studies of F-12 to rats (see Section XII, C, Chronic Toxicity), no abnormalities were noted in fertility, gestation, viability and lactation indices (Sherman, 1974). Further, pregnant rats have been intubated with F-12 at levels of 16.6 and 170.9 mg/kg/day from day six to day fifteen of their gestation. No effects were noted in embrional development or abnormalities in live fetuses (Culik, 1973).

G. Mutagenicity

As with teratogenicity, the fluorocarbons have not been implicated in mutagenicity. Sherman (1974) has determined the mutation rates in rats during a two-year feeding study. The results are summarized in Table LXXXV. Sherman (1974) indicates that mutation rate increases of less than +25% are not significant.

Table LXXXV. Effects of Freon® 12 Administered Orally to the Parent Female and Male Rats on Fertilization, Implantation and early Development of the Fetuses - Dominant Lethal Effects

[illegible]6966 - MR-1[illegible]

	I (Control)	II (Control)	Low Level Freon® 12	High Level Freon® 12	Standard Values (Range) for Charles River (CD) rats (1)
No. of Females Bred	19	20	20	19	
No. of Females Pregnant (Fertility Index)	17 (89.5)	20 (100)	18 (90)	17 (89.5)	90 ([illegible]-100)
No. of Live Fetuses	200	130	160	178	
No. of Dead Fetuses	0	0	0	0	
No. of Live Fetuses/Litter	11.8	6.5	8.9	[illegible]	[illegible]
Total No. of Corpora Lutea	[illegible]	[illegible]	[illegible]	[illegible]	
No. of Corpora Lutea/Pregnant Female	16.[illegible]	13.9	14.9	[illegible]	
No. of Implantation Sites	254	251	258	[illegible]	
No. of Implantation Sites/Preg. Female	14.9	12.6	14.3	12.6	12.9 ([illegible]-14.1)
No. of Early Resorption Sites (Deciduomata)	[illegible]	102	87	74	
No. of Late Resorption Sites	19	19	11	[illegible]	
Total Number of Resorptions	54	121	98	54	
Preimplantation Loss (2)	8.0%	9.4%	4.1%	[illegible]	
Mutation Rate (3)	1[illegible].9%	40.6%	33.7%	1[illegible]%	
Mutation Rate Compared With Control I (4)			4.6	11.1	
Mutation Rate Compared With Control II (4)			-[illegible]	-[illegible]	

(1) Personal communication; unpublished data obtained from Charles River Breeding Labs., Wilmington, Mass. for period [illegible].

(2) Preimplantation loss: $\frac{\text{Number of Corpora Lutea - Number of Implantation Sites}}{\text{Number of Corpora Lutea}} \times 100$

(3) Mutation Rate: $\frac{\text{Number of Early Resorption Sites (Deciduomata)}}{\text{Number of Implantation Sites}} \times 100$

(4) Mutation Rate: $\left(100 - \frac{\text{Number of Live Fetuses/Litter of Test Group}}{\text{Number of Live Fetuses/Litter of Control Group}} \times 100\right)$

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H. Carcinogenicity

Fluorocarbon-112 and F-113 at doses of 0.1 ml 10% (V/V) solution injected subcutaneously in the neck of neonatal mice are not carcinogenic. However, when injected in conjunction with a 5% (V/V) solution of piperonyl butoxide, hepatomas are induced in male mice as indicated in Table LXXXVI. This is particularly marked with F-113.

Table LXXXVI. Tumors Induced in Swiss Mice by Injection of "Freons" and Piperonyl Butoxide Shortly After Birth [from Epstein *et al.*, 1967]

Treatment Group	Sex	No. of mice, subsequently autopsied, alive at the beginning of each period (No. at risk)					No.	[illegible] No. tumors in each period as % of No. of mice at risk				No.	Malignant lymphomas No. tumors in each period as % of No. of mice at risk			
		Weeks						Weeks					Weeks			
		11-20	21-30	31-40	41-50	51+		21-30	31-40	41-50	51+		21-30	31-40	41-50	51+
Solvent controls	M	72	68	59	55	48	4	0	[illegible]	9	[illegible]	1	0	0	0	2
	F	69	69	69	68	68	0	0	0	0	0	0	0	0	0	0
"Freon" 11	M	25	25	22	21	21	2*	0	0	[illegible]	10	1	4	0	0	0
	F	20	20	20	20	20	0	0	0	[illegible]	0	0	0	0	0	0
"Freon" 112	M	27	27	27	20	17	0	0	0	0	0	0	0	0	0	0
	F	22	22	21	20	19	0	0	0	0	[illegible]	0	0	0	0	0
"Freon" 113	M	29	29	23	26	21	1	0	0	[illegible]	5	0	0	0	0	0
	F	21	21	20	20	20	0	0	[illegible]	0	0	[illegible]	0	0	0	5
Piperonyl butoxide	M	40	38	35	25	20	0	0	[illegible]	[illegible]	[illegible]	0	0	0	0	0
	F	36	36	36	36	36	0	0	[illegible]	[illegible]	[illegible]	0	0	0	0	0
"Freon" 112 and piperonyl butoxide	M	30	26	26	14	13	5	0	3	[illegible]	14	0	0	0	0	0
	F	29	29	28	25	24	0	0	0	[illegible]	0	1	0	4	0	8
"Freon" 113 and piperonyl butoxide	M	25	24	24	19	18	3	0	[illegible]	[illegible]	17	0	0	0	0	0
	F	24	24	24	24	24	0	0	0	[illegible]	0	1	0	0	0	4

* One of these also had a pulmonary adenoma.

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The apparent synergestic hepatocarcinogenicity of these fluorocarbons with piperonyl butoxide cannot be explained at present. Long before the tumors appeared, the fluorocarbons should have been eliminated from the rats' bodies. The investigators speculate that piperonyl butoxide may interfere with the metabolism of these fluorocarbons (Epstein *et al.*, 1967a).

The significance of this effect is difficult to interpret because of the lack of follow-up studies in other species (Tomatis *et al.*, 1953) and other fluorocarbons. The results of Epstein and coworkers (1967a), however, have not been disputed in the literature (e.g., Friedman *et al.*, 1972; Jaffe *et al.*,1969; Kamienski and Murphy, 1971; Redfern *et al.*, 1971; Vogel and Zaldivar, 1971). The increased susceptibility of males to liver tumors is common for chemical carcinogens (Roe and Grant, 1970). The use of newborn mice as experimental animals in screening for carcinogenicity is widely accepted as having valid predictive value (Epstein *et al.*, 1970; Della Porta and Terracini, 1969; Tomatis *et al.*, 1973) although this acceptance is not universal (Grasso and Crampton, 1972).

On the basis of the study by Epstein and coworkers (1967a), "Freons" have been listed as chemicals inducing tumors in the liver of mice (Tomatis *et al.*, 1973). This is misleading. Only F-112 and F-113 have been tested. A significant increase in hepatomas are induced only with piperonyl butoxide. Piperonyl butoxide is a potent inhibitor of microsomal enzyme function (detoxification) in insects and is thus a useful synergist with insecticides greatly reducing the amount of insecticides that are necessary for insect control (Casida, 1970; Cooney *et al.*, 1972). The compound is thermally and photochemically stable under conditions of normal use (Friedman and Epstein, 1970; Fishbein and Gaibel, 1971). However, the potential hazard posed by piperonyl butoxide and fluorocarbons has been demonstrated in only the most preliminary manner. Fluorocarbons-112 and F-113 are not commonly used in preparations containing piperonyl butoxide (McCaul, 1971). While piperonyl butoxide has been shown to greatly inhibit microsomal enzyme systems in mice, it is much less potent in rats and man (Conney et al., 1972). Thus, the most that can be concluded on the basis of current information is that fluorocarbon propellants may require testing in conjunction with microsomal inhibitors for potential carcinogenic activity (McCaul, 1971). If microsomal enzyme inhibitors are shown to induce liver tumors with the fluorocarbons, this information might lead to a better understanding of fluorocarbon metabolism.

The precancerous lung cell changes noted by Good (1974) are discussed in Section XI, B, Human Toxicity, Occupational Exposure and Normal Use.

I. Behavioral Effects

Apart from the effects of intoxication and anesthesia as discussed in previous sections, no behavioral effects have been attributed to these fluorocarbons in non-human mammals and birds. The work of Carter and coworkers (1970b) may be considered an exception. Exposure to 20-25% E-1301 significantly decreased the performance of trained monkeys. This operant behavior was completely disrupted at higher concentrations without signs of CNS depression or analgesia.

J. Possible Synergisms

The synergistic carcinogenicity of F-112 and F-113 have been noted in Part G, Carcinogenicity. Epstein and coworkers (1967a and b) have also noted synergistic toxicity of these compounds in mice. As indicated in Table LXXXVII, mortality occurred primarily in the first week and was significantly higher in mice receiving both piperonyl butoxide with F-112 or F-113 than in those groups receiving F-112 or F-113 alone.

Table LXXXVII. Toxicity Induced in Swiss Mice by Neonatal and Perinatal Subcutaneous Injections of F-112 and F-113 Alone and in Combination with a 'Synergist', Piperonyl Butoxide (Epstein et al., 1967b)

Drug and concentration in tricaprylin (% v/v)	Drug Dosage on Specified Days (ml or mg)				Total Drug dosage	Initial no. mice injected (litters)	% Mortality (no. survivors) at specified days			% Males among survivors at weaning	Ave. weight (g) of mice at specified days			
	1	7	14	21			7	21	[illegible]		1	7	14	21
Tricaprylin (only)(solvent controls)	-	-	-	-	-	170 (16)	9(154)	[illegible]	[illegible]	-	[illegible]	[illegible]	[illegible]	13.[illegible]
Tricaprylin (only) (control)	-	-	-	-	-	140 (10)	14(95)	[illegible]	[illegible]	51	1.7	[illegible]	[illegible]	[illegible]
'Freon' 112 (10%) alone	0.1	0.1	0.2	0.2 ml	0.6 ml	56 (5)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8.8	13.2
'Freon' 112 (10%) with PB	0.1	0.1	0.2	0.2 ml	0.6 ml	137 (12)	[illegible]	[illegible]	[illegible]	[illegible]	1.7	[illegible]	10.7	16.4
'Freon' 113 (10%) alone	0.1	0.1	0.2	0.2 ml	0.6 ml	52 (4)	[illegible]	[illegible]	[illegible]	59	1.6	[illegible]	[illegible]	14.2
'Freon' 113 (10%) with PB	0.1	0.1	0.2	0.2 ml	0.6 ml	96 (8)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9.8	15.0

0.1 ml of 5% synergist in tricaprylin injected on days 1 & 7 and 0.2 ml on days 14 & 21; groups not receiving synergist were injected with drug alone in corresponding volumes of tricaprylin at the same intervals.

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The increases in average weight gains in fluorocarbon with piperonyl butoxide exposed animals is not readily explained and is termed "anomalous" by Epstein and coworkers (1967b). Preferential male survival was not noted and thus is not a factor in this weight gain. However, it seems probable that in a given group of animals administered toxic compounds, the more vigorous animals would survive and this group of survivors might be expected to show increased weight gain over a control group. Thus, the increased weight gain of the fluorocarbon/piperonyl butoxide exposed group might be an artifact of experimental design.

The possible potentiating effect of F-22 and F-115 in causing cardiac arrhythmias by sensitization to exogenous epinephrine has been discussed (see Section XII, Part D-1).

As with the parallel study on the synergistic carcinogenicity of F-112 and F-113, the above information on synergistic toxicity is quite limited. However, the interactions of environment pollutants is an area of legitimate concern (Cooney and Burns, 1972). The possibility of such reactions involving fluorocarbons cannot be ruled out on the basis of their presumed low level of biological activity and more experimental work in this field is warranted, particularly in that fluorocarbons are often used or administered with compounds of known biological activity (McCaul, 1971).

XIII. TOXICITY TO LOWER ANIMALS

No information on the toxicity of fluorocarbons to non-mammalian vertebrates or any of the Metazoan Phyla has been encountered.

XIV. TOXICITY TO PLANTS

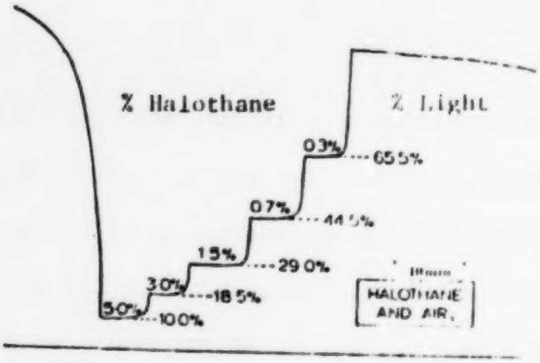
Of the fluorocarbon propellants, solvents, and fire extinguishing agents, only F-11 and F-12 have been studied for phytotoxicity. Taylor (1974) has exposed plants to F-11 and F-12 at concentrations of 0.5-1, 10, and 15 ppm for two weeks. No signs of toxicity, impaired growth, or absorption were noted.

Halothane has been shown to cause metaphase arrest in the root tips of Vicia faba, the European broad bean. The ED_{50} ranges from 0.5-0.9%. Total arrest is achieved with 2.0% over 8 hours (Nunn *et al.* 1971).

XV. TOXICITY TO MICROORGANISMS

Similar to its effect in Vicia faba (Nunn et al., 1971), halothane has been shown to cause reversible microtubular disruption at 2% concentration over a 7 minute period in Actinosphaerium nucleofilum, a heliozoan protozoa (Allison et al., 1970) and decrease the bioluminescence of Photobacterium phosphoreum at concentrations as low as 0.3% (White and Dundas, 1970). The latter effect has also been noted for F-22 although the potency of this fluorocarbon (ED_{50}, 37.6%) is much less than that of halothane (ED_{50}, 0.76%). Dose-response data for these compounds and a number of others screened for their effect on bioluminescence are given in Table LXXXVIII.

Table LXXXVIII. Mean dose-response curves for halothane (HAL), F-22, and a variety of other agents on bioluminescence in Photobacterium phosphoreum (White and Dundas, 1970); reprinted with permission from D.C. White, Copyright 1970, MacMillan Journals Ltd.



The investigators suggest that this may be a simple, inexpensive, sensitive screening test for determining the potency of compounds with anesthetic activity and synergistic effects (White and Dundas, 1970). In this respect, it is interesting to note that F-22 ED_{50} of 37.6% is quite close to its ALC in mice, 40% x 2 hours (see Table L). This may well be coincidental. Halsey and Smith (1970) conducted similar tests in the same bacteria. The results obtained for ED_{50}s in bacteria compare well with those of AD_{50}s (dose causing general anesthesia) in mice as summarized in Table LXXXIX.

Table LXXXIX. Comparison of the ED_{50}s of bioluminescence inhibition in bacteria and the AD_{50}s in Mice for Halothane, F-22 and F-12 (from Halsey and Smith, 1970).

Compound	ED_{50} (atmospheres)	AD_{50} (atmospheres)
Halothane	0.0081 ± 0.0001	0.0086
F-22	0.209 ± 0.004	0.16 ± 0.05
F-12	0.50 ± 0.01	0.40 ± 0.06

The comparative potencies of F-22 and F-12 compare well with those of the toxic effects described in mammals (see Section XII , Mammalian Toxicity). Halsey and Smith (1970) further note that site of action in these compounds is probably hydrophobic in that potencies correlate better with oil/gas partition coefficients than with hydrate dissociation pressures.

Stephens and coworkers (1970) have proposed a somewhat different system for assessing the biological effects of various gases. They have exposed Neurospora crassa - the common bread mold- to a variety of compounds including F-12 and observed for changes in conidia formation, perithecia production, and mutagenicity. Exposures to gas mixture (in oxygen) were 30 ml/minute for 10 minutes - to evacuate air - to innoculations of five-day old micro-conidia of opposite mating types. The cultures were then incubated in a specified gas atmosphere for 21 days. Phenotypically, F-12 at concentrations of 50%, 75%, and 100% resulted in light white conidia 48 hours after exposure. Normal conidia are heavy pink and 100% oxygen controls caused light pink conidia. Perithecial formation was not inhibited during any of the exposures to F-12. However, exposure to 75% F-12 resulted in a mutation rate of 0.33% and 50% F-12 in a rate of 1.42%. The normal mutation rates for this species is 0.066% to 0.28% and the control rate was 0.13% with no mutations noted in the 100% oxygen control. Because mutation rates had to be determined on the basis of crosses producing ripe ascospores, only the 50% F-12 exposure shows significant mutagenic activity. The same species exposed to F-23 for 18 hr. at 4°C produced 4.7% yellow, cauliflower, colonial mutants. No mutants were noted in air or oxygen controls. As Stephens and coworkers (1970) indicate, this type of testing is rather new and its significance to other areas of fluorocarbon toxicity cannot yet be defined.

The comparative toxicity of F-12 and F-142b have been determined in liquid and vapor states for a variety of microorganisms (Prior et al., 1970). Of the eighteen species tested, seven species grew as well in contact with gaseous F-12 or F-142b as in their absence (different groups for each fluorocarbon). In no instances were substantial growth reductions noted. However, in the liquid state both F-12 and F-142b substantially reduced cell viability in all cultures tested. Because agitation is required to induce the toxic effects, Prior and coworkers (197) conclude that there is probably some interaction between the compounds and the lipids in the microorganisms and cite a study which attributes the toxic effect of F-11 on Pseudomonas striata to its strong lipophilic characteristics (Lie, 1966). This is in agreement with mammalian studies which indicate binding with the lipid portions of membrane systems as a mechanism of biological activity.

Reed and Dychdala (1964) have exposed three bacteria and two fungi to a mixture of F-12 and F-114 (40/60) The bacteria were incubated for 48 hours and growth determined by visual examination. Two aerobic species - Pseudomonas aeruginosa and Staphylocuccus aureus - were not affected. However, Streplococcus agalactiae (anaerobic), Aspergillus niger, and Paecilomyces varioti failed to grow. The investigators did not attribute this to fluorocarbon toxicity. Rather, they reasoned that the anerobe was denied sufficient CO_2 and the aerobic fungi denied sufficient oxygen by the addition of the propellant (displacement) or the formation of a stratified layer of fluorocarbons between the culture media and the air in the container.

XVI. CURRENT REGULATION

Regulations at all levels of government are currently under review and evaluation (Hanavan, 1974). With the exception of FDA regulations on the use of F-12, F-115, and C-318 (octa-fluorocyclobutane), regulations of any type (federal, state, county, foreign, etc.) have not been encountered.

Fluorocarbon-12 has been approved as a food additive provided that it is 99.97% pure and that it is used only as a direct-contact freezing agent for foods. The container must be labelled "dichlorodifluoromethane," designated as food grade and contain instructions for use (Federal Register, 1967). Fluorocarbon-115 may also be used as a food additive provided that it is 99.97% pure and contains less than 10 ppm unsaturated fluorocarbons and 200 ppm saturated fluorocarbons. It may be used with carbon dioxide, nitrous oxide, propane and/or C-318 as a propellant and aerating agent for most sprayed or foamed foods. The label must contain the name chloropentafluoroethane, specify the percentage of a mixture, be designated food grade, and contain proper instructions for use (Federal Register, 1965). Similar approval has been given to C-318 except that the purity must be 99.99% and contain less than 0.1 ppm fluoroolefins calculated as perfluoroisobutylene (Federal Register, 1965).

The DuPont de Nemours and Company's Corpus Christi plant in Ingleside, Texas, has requested and been granted exemption of the following fluorocarbons from Regulation V under the Texas Clean Air Act (Borden, 1973): F-11, F-12, F-13, F-14, F-21, F-22, F-23, F-113, F-114, F-115, and F-116.

Because they are shipped in pressurized containers, fluorocarbons must be shipped in containers meeting ICC requirements for compressed gases (DuPont, 1973).

XVII. CONSENSUS AND SIMILAR STANDARDS

Two standards are commonly employed in classifying exposure limits to the fluorocarbons: these are Threshold Limit Values (TLVs) and the Underwriters' Laboratories Classification. TLV's are assigned by the American Conference of Governmental Industrial Hygienists. Most of the current values were assigned in 1968, but periodic updates are made if warranted by new information. The values, usually expressed in parts per million, represent the maximum concentration that should be present in the working environment. In cases where toxicological information would indicate high acceptable concentration, these values are based on good manufacturing practice. Concentrations higher than 1000 ppm for any compound being used indicate poor production or handling technique and thus this concentration is the upper limit of acceptability. The definitions by the Underwriters' Laboratories in their classification are given in Table XC.

Table XC. Underwriters' Laboratories Comparative Toxicity Classification of Refrigerants (Underwriter's Laboratories, 1971a)

Toxicity Group	Concentration Per Cent by Volume	Duration of Exposure to Produce Death or Serious Injury to Test Animals
1	½ to 1	5 minutes
2	½ to 1	½ hour
3	2 to 2½	1 hour
4	2 to 2½	2 hours
5	Intermediate between Groups 4 and 6	
6	20	No injury after 2 hours

The Underwriters' Laboratories Classification and TLVs for the various fluorocarbons under consideration in this review are given in Table XCI.

Table XCI. TLVs and Underwriters' Laboratories Classification for Various Fluorocarbons.

Compound	Code	Threshold Limit Value[1]	Underwriters' Laboratories Classification[2]
$CC\ell_3F$	F-11	1000*	5
$CC\ell_2F_2$	F-12	1000	6
$CC\ell F_3$	F-13	(1000)*	6
CF_4	F-14	(1000)*	6
$CHC\ell_2F$	F-21	1000	4-5
$CHC\ell F_2$	F-22	(1000)	5
$CC\ell_2F-CC\ell_2F$	F-112	500	
$CC\ell_3-CC\ell F_2$	F-112a	500	
$CC\ell F_2-CC\ell_2F$	F-113	1000	4-5
$CC\ell F_2-CC\ell F_2$	F-114	1000	6
$CC\ell F_2-CF_3$	F-115		6
$CC\ell F_2Br$	H-1211		5^+
CF_3Br	H-1301	1000	6^+
$CBrF_2-CBrF_2$	H-2402		5^+

[1] A.C.G.I.H., 1973; * Clayton, 1970

[2] Underwriters' Laboratories, 1971a; + Underwriters' Laboratories, 1971b

XVIII. Fluorocarbons: Summary and Conclusions

The fluoromethanes and fluoroethanes are widely used as aerosol propellants, solvents, fire extinguishing agents, and refrigerant gases. Current world production is probably approaching two billion pounds per year with an annual growth potential of approximately 6-8 percent. About half of the production and use is currently centered in the United States. The commercial success and continued growth rate of these fluorocarbons are predicated largely on the suitability of their physiochemical properties to the above uses and their relatively low level of demonstrated toxicity. As a result of their commercial success and use patterns, these fluorocarbons are and will continue to be ubiquitous atmospheric contaminants with average concentrations (v/v) in the low (2-15) ppb range and peak concentrations in low (20-30) ppm range are projected for the next half century. Adverse biological effects from exposure to such levels cannot be demonstrated from the available toxicity data. However, fluorocarbons are not biologically inert and the effects of long-term low-level continuous exposures have not been extensively characterized.

This study concluded that in 1972 approximately 711 x 10^6 lbs of the 900 x 10^6 lbs produced in the United States was released to the environment. Global release is perhaps twice that figure. Of the fluorocarbons under study, F-12, F-11, and F-22 constitute more than 75% of the total market and present the major sources of fluorocarbon environmental contamination. Fluorocarbon-11 and F-12 have already been monitored at background levels in the 100-500 ppt range. This monitoring data supports the fact that the fluorocarbons are extremely persistant, based upon what is known about the physical, chemical and biological stability of the C-F bond and some experimental evidence.

Fluorocarbon use patterns suggest increasing concentrations going from the background environment, to urban areas, to human dwellings. This pattern is also supported by monitoring data indicating fluorocarbon concentrations in homes may vary in the 200ppt-500,000 ppt range, the wide fluctuations reflecting the sporatic use of aerosols and leaks from refrigerant applications.

The potential hazards posed by the large scale atmospheric release of fluorocarbons can be anthropocentrically divided into two general classes: direct hazard to man through exposure to comparatively high concentrations found in the home or peak concentrations in urban areas: or indirect hazard to man due to adverse effects from long-term low-level exposure to man or other ecologically important species. It must be emphasized that the maximum peak concentrations of total fluorocarbons will probably not exceed 20 ppm and the maximum background concentrations will probably not exceed 15 ppb. There is absolutely no direct evidence that such levels are in any way detrimental to any living systems. However, the effect of long-term, low-level, continuous exposure to fluorocarbons is virtually unexplored. The effect of fluorocarbons on non-mammalian species has also received very little study. Lastly, the pharmacology and toxicology of these compounds has only recently generated intense investigation and these investigations are leading to an extensive reevaluation of fluorocarbon biological activity. Thus, the type rather than the amount of toxicity data available prevents the characterization of fluorocarbons as environmentally innocuous.

Given the lack of direct evidence that fluorocarbons may be harmful at environmentally probable concentrations and the inappropriateness of most current toxicity data in evaluating environmental hazard, certain facets of fluorocarbon toxicology suggest the need for further definition. When fluorocarbons were first introduced as aerosol propellants, they were considered biologically inert. Subsequent investigations, however, revealed a broad spectrum of cardiovascular effects. That fluorocarbons may have other unrecognized biological effects cannot be ruled out. Up until quite recently, the stability of the C-F bond was thought to preclude metabolism. However, there is now a reasonable indication that F-12 is slightly metabolized after a relatively short exposure. If F-12 is metabolized, then F-11 may also be metabolized. The rates of metabolism and the significance of this metabolism at environmental concentrations are unknown. Lastly, only two continuous chronic exposures have been conducted with fluorocarbons (see p. 151). One study clearly indicated liver damage in guinea pigs at a concentration (810 ppm) usually considered innocuous. While not suggesting that such damage is typical of fluorocarbon exposure at environmentally probable concentrations, the inadequacies of predicting long-term effects on the basis of short-term exposures is apparent.

An additional factor which requires further investigation is that fluorocarbons may migrate to the upper atmosphere and reduce the ozone layer (chlorine atom released from the fluorocarbon would react with ozone), thus allowing high energy ultraviolet irradiation to reach the earth's surface. Reductions in the ozone layer have been correlated with increases in skin cancer. Since this possible effect has only recently been reported (see Anon., 1974d and 1974e; Cicerone et al., 1974), a detailed description of the effect is not included in the text of this report. Reference should be made to the cited papers. This possible affect is under investigation and may prove to be the greatest environmental hazard from commercial use of fluorocarbons. However, presently, no monitoring of fluorocarbons in the upper atmosphere has been reported and the relative importance of fluorocarbons in terms of catalyzing ozone decomposition is unknown.

Thus, considering the projected levels of fluorocarbon contamination along with what is known of their biological effects, fluorocarbons do not seem to present anything approaching an imminent environmental threat. The levels projected in this study are not likely to be exceeded, and, depending upon the economics and availability of raw materials (e.g. CaF_2-fluorspar), the actual levels may be much lower. Fluorocarbon toxicology is currently being investigated by a number of research groups and - given the use of fluorocarbons in pharmaceutical preparations, the potential for abusive inhalation, and the vague possibility of occupational hazard - such research will probably continue for many years. However, the data of Cicerone et al. (1974) suggest that the possibility of fluorocarbons catalyzing ozone destruction should be resolved relatively soon before the rate of ozone destruction by natural sinks is exceeded.

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